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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1934

ORIGINAL ARTICLES.

THE MECHANISM OF THE INCREASED FRAGILITY OF THE ERYTHROCYTES IN CONGENITAL HEMOLYTIC JAUNDICE.

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Congenital hemolytic icterus is characterized clinically by anemia, non-obstructive jaundice and enlargement of the spleen. The erythrocytes show constant microcytosis (small diameter), an increase in reticulocytes and a decreased resistance to hypotonic salt solutions. The anemia is caused by the increased blood destruction resulting from the abnormal fragility of the red cells, the jaundice is due to the rapid formation of bile pigments from the released hemoglobin beyond the excretory capacity of the liver; the spleen is enlarged because of the great increase in its phagocytic activity; the reticulocytosis is an expression of the overstimulation of the bone marrow in attempting to compensate for the rapid destruction of erythrocytes. The anemia, the jaundice, the splenomegaly and the reticulocytosis are thus all secondary to the increased blood destruction.

The two characteristic changes in the erythrocyte, microcytosis and increased fragility, have been noted by all careful students of the disease, although there is no unanimity of opinion concerning the cause and the interrelation of these two findings. The observation of microcytosis has usually been based on finding a decrease in the mean cell diameter on measurement or the obvious smallness of the cells on examination of a stained blood film. Little attention has been given to the actual volume of the cell, since very few measurements of the mean corpuscular volume and thickness have been made.

Naegeli[1] found in 11 patients a mean corpuscular volume of 100 cubic microns (his normal, 88 cubic microns), von Boros,[2] a mean of 85 in 8 cases (his normal, 91), and Gänsslen,[3] a volume of 92, 95 and 111 cubic microns in 3 cases. The diameter of the mean cell is decreased out of proportion to the change in volume, so it is apparent that the thickness of the cell must be increased, and the cell must tend to a spherical instead of biconcave shape. Naegeli[1] thinks that the presence of erythrocytes of decreased diameter and increased thickness is a constant and fundamental variation from normal in patients with congenital hemolytic icterus, representing the inherited feature of the disease and indicating a distinct type of human species. Such cells he designates spherocytes to denote their characteristic globular form and as synonyms for congenital hemolytic anemia he uses the terms, "spherocyte anemia" and "globe-cell anemia."

Other observers have said little about the increased thickness of the erythrocyte and offer varying explanations for the microcytosis. Chauffard,[4] who first noted this type of cell, regarded the small size as well as the increased fragility as an expression of the lessened vitality of the cells. Meulengracht[5] is inclined to the view that the microcytosis and increased fragility are regeneration phenomena secondary to the increased bone-marrow activity. Von Boros[2] finds thick microcytes in conditions other than congenital hemolytic jaundice, and hence does not regard them as characteristic of the disease. Gänsslen[3] considers the primary defect in the marrow, making it incapable of supplying cells of normal size and resistance.

While microcytosis is almost an invariable finding, only Naegeli and von Boros have considered the frequency and degree of spherocytosis. Naegeli records no measurements of cell thickness in his cases, although he recognized this as increased. Von Boros[6] gives a line chart for calculating cell thickness from the measured diameter and corpuscular volume and also evolves a formula for calculating the volume of the mean cell from the measured mean diameter when changes in the diameter and thickness are proportional and parallel. To indicate the degree of change in thickness he suggests a "thickness index" which is calculated by dividing the mean corpuscular volume (as determined directly from the red cell count and the hematocrit reading) by the mean corpuscular volume (as calculated by his formula from the measured mean diameter) when the decrease in thickness is proportional to the decrease in diameter. Since this index records not only the thickness relative to normal but considers the volume as well, it is best called the "volume-thickness index." The rather laborious calculation of this index by the method of von Boros may be simplified by using a nomogram[7] in which the volume index (volume of the mean cell relative to normal) corresponding to any mean cell diameter is indicated. Thus, from the nomogram the volume index corresponding to a mean

cell diameter of 6.41 microns is 0.581 if the thickness is decreased in the same proportion as the diameter. This figure multiplied by 90, the normal mean corpuscular volume in my series, gives a calculated mean corpuscular volume of 52 cubic microns for a mean cell diameter of 6.41 microns. The measured mean corpuscular volume in this instance was 78 cubic microns. The volume-thickness index (V.-T. I.) is then 78/52 = 1.50. Von Boros calculated this index in 8 patients with congenital hemolytic icterus and found it increased in 4 and within normal limits in 4.

To determine the frequency and degree of spherocytosis in my series of cases of congenital hemolytic jaundice, I have measured the mean corpuscular volume, the mean cell diameter and calculated the volume-thickness index in 10 patients with an active form of the disease and in 2 patients after splenectomy (Table 1).

TABLE 1.—SIZE AND SHAPE OF ERYTHROCYTES IN CONGENITAL HEMOLYTIC JAUNDICE.

Patient.	Diagnosis.	Measured mean erythrocyte volume (A), cubic microns.	Measured diameter, microns.	Calculated thickness, microns.	Calculated mean erythrocyte volume from measured diameter (C), cubic microns	Volume-thickness index, A/C.
1	Normal	90	7.70	1.95	90	1.00
2	Congenital hemolytic jaundice	160	6.41	4.75	52	3.10
3	Congenital hemolytic jaundice	77	6.40	2.40	52	1.50
*		78	6.67	2.25	59	1.32
4	Congenital hemolytic jaundice	90	6.18	3.00	47	1.92
5†	Congenital hemolytic jaundice	87	6.55	2.60	55	1.60
6	Congenital hemolytic jaundice	110	6.50	3.30	54	2.00
7	Congenital hemolytic jaundice	87	6.94	2.30	66	1.35
8	Congenital hemolytic jaundice	90	7.05	2.30	68	1.32
9	Congenital hemolytic jaundice	86	7.18	2.18	70	1.23
10	Congenital hemolytic jaundice	108	7.41	2.50	79	1.36
11	Congenital hemolytic jaundice	102	7.18	2.52	70	1.45
12	Congenital hemolytic jaundice	72	6.10	2.75	45	1.60
13	Obstructive jaundice	93	8.17	1.80	105	0.89
14	Obstructive jaundice	91	8.57	1.60	126	0.73
15	Pernicious anemia	130	8.84	2.10	140	0.93
16	Pernicious anemia	135	8.89	2.20	141	0.96
17	Idiopathic microcytic anemia	63	7.07	1.60	70	0.90
18	Idiopathic microcytic anemia	59	6.68	1.70	59	1.00

* Same patient 3 months after splenectomy.
† Six years after splenectomy.

In every instance the mean cell diameter is decreased and the volume-thickness index is increased, although the mean corpuscular volume is variable. In simple microcytic anemia and pernicious anemia the index is normal; in obstructive jaundice it is decreased, since the mean diameter is usually increased without a correspond-

ing increase in mean corpuscular volume. The characteristic findings are best illustrated by a diagram showing a cross-section view of the mean cell in these different clinical conditions (Fig. 1). In 2 patients studied after splenectomy the microcytosis and increased volume-thickness index have persisted, although the jaundice and anemia have disappeared.

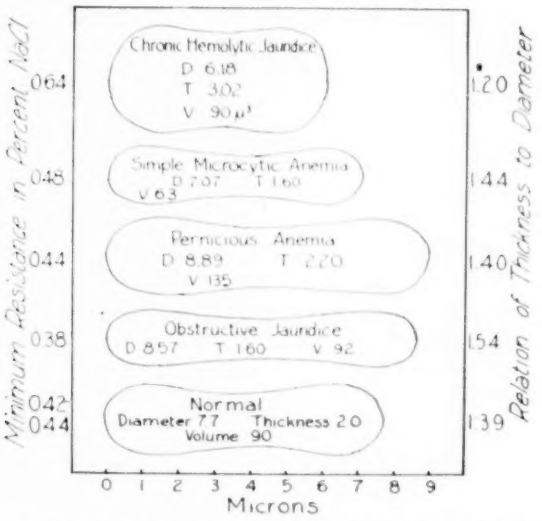

FIG. 1. - Cross-section and measurements of mean erythrocyte in different clinical conditions.

It seems apparent from my results that Naegeli's conception of microspherocytosis as the fundamental and probably constant inborn error in this disease seems the correct one. This abnormal shape of the red cell evidently represents an anatomic variation from normal, just as do the tower skull and other physical abnormalities frequently observed in congenital hemolytic jaundice. It is also apparent that the determination of the volume-thickness index is a most valuable procedure in the diagnostic study of doubtful cases of congenital hemolytic jaundice, since the index is constantly increased here and rarely, if ever, in other confusing clinical conditions. The persistence of microspherocytosis after splenectomy is of importance also in evaluating this variation from normal in the shape of the cell as the primary feature of the disease.

Although the microspherocytosis and the increased fragility are constant and the only fundamental features in the disease, no one has proved a direct relationship between these two phenomena. Naegeli[1] regards both as constitutional and caused by the fundamentally different cell structure; Gänsslen[8] thinks both are evidence of a primary defect in the bone marrow, and suggests that

the microspherocytes by reason of their increased thickness absorb water more readily from a hypotonic solution. Von Boros points out, however, that the capacity for absorption is less, instead of more, since such cells have a small surface in relation to volume. Meulengracht[5] has discussed the parallelism of the two findings, but concludes there is no relation between them. I have made some experiments which indicate that the increased fragility is dependent on the spherocytosis or altered shape of the cells which affords a possible explanation for the increased hemolysis characteristic of the disease.

In the lower animals the volume and diameter of the erythrocytes varies greatly, while the thickness is much the same. Emmons'[9] measurements of all dimensions of the red cell in the dog, rabbit, cat and goat, and Vallery-Radot's[10] determination of the resistance of the red cells to hypotonic salt solutions for the same group of animals, are summarized in Table 2 and shown graphically in cross-section in Fig. 2. As the cell changes toward a globular shape in different species, the resistance of the cells to hypotonic saline solution decreases in almost direct proportion, so there seems a definite relation between the tendency to spherocytosis and increased fragility in lower animals.

TABLE 2.—RELATION OF SIZE AND SHAPE OF ERYTHROCYTES TO RESISTANCE TO HYPOTONIC SOLUTIONS.*

	Diameter.	Thickness.	Volume.	Relation of thickness to diameter.	Resistance, % NaCl.
Man	7.8	1.84	88	1 : 4.2	0.42–0.48
Dog	7.2	1.70	69	1 : 4.2	0.50–0.54
Rabbit	6.6	1.84	63	1 : 3.6	0.52–0.54
Cat	5.6	1.75	43	1 : 3.2	0.60–0.66
Goat	4.0	1.95	25	1 : 2.1	0.72–0.74

* Measurements from W. F. Emmons;[9] fragility tests from Vallery-Radot.[10]

To obtain further information on this point I have determined the shape of the red cell of man when placed in hypotonic salt solutions. Heparinized blood was pipetted in aliquot amounts into a series of graduated centrifuge tubes, quickly centrifugalized and distilled water in varying amounts was added to the supernatant plasma. After thorough mixing, the cells were again suspended in the diluted plasma, the tubes allowed to stand for 1 hour, films made on cover glasses from the diluted blood and tubes again were centrifugalized to determine the changes in volume of the cells. A red cell count was done and the mean corpuscular volume for each dilution was calculated. The tube in which hemolysis began was noted. The mean cell diameter in each tube was determined by measuring 200 cells on the stained film and the thickness cal-

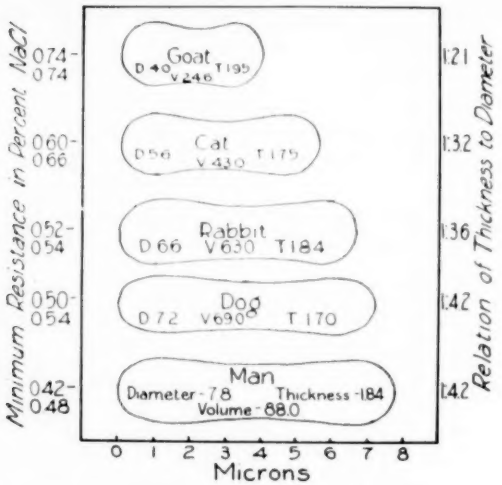

FIG. 2.—Cross-sections and measurements of the mean in different animals in relation to fragility.

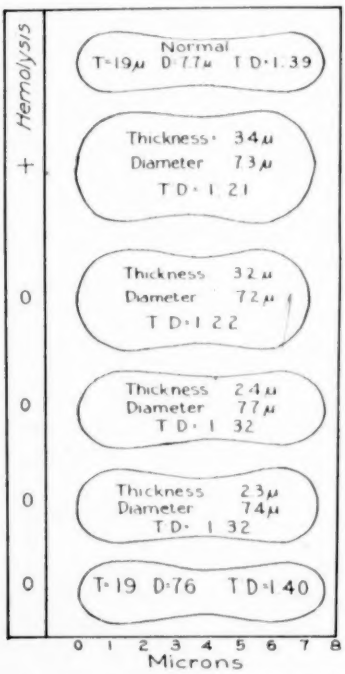

FIG. 3.—Changes in the shape and measurements of the mean erythrocyte of normal blood on the addition of varying amounts (Table 3) of distilled water to the plasma.

culated from von Boros' chart. The progressive change in shape in the cells of normal blood so treated is shown in Fig. 3. The changes in diameter are slight, while the variation in volume is slight, so the cells become thicker and globular. At a certain point hemolysis begins. Hamburger[11] found long ago that the erythrocytes of the horse and dog decrease in diameter as the plasma is diluted with distilled water, and pointed out that the cells so treated become globular. Ponder[12] found a similar decrease in the diameter of the cells of man in hypotonic salt solution. Pijper,[13] on the contrary, reports an increased diameter in hypotonic solutions. I can find on record no measurement of the volume and thickness of the erythrocytes of man in relation to diameter when placed in hypotonic salt solutions.

Since the characteristic variation of the erythrocyte from normal in congenital hemolytic jaundice is a decreased diameter with increased thickness, it is apparent that much less dilution of the plasma in which such cells are suspended should be necessary to bring them to the shape at which hemolysis takes place. For, at the beginning, the shape of the cells already corresponds to one of the stages through which a normal blood must pass when placed in successive dilutions of plasma. The experiment made with normal blood was repeated with blood from a mild and from a severe case of congenital hemolytic jaundice (Table 3 and Fig. 4).

TABLE 3.—SIZE AND SHAPE OF ERYTHROCYTES ON ADDITION OF DISTILLED WATER TO PLASMA.

Patient.	Tube No. (5 cc. blood in each tube).	Distilled water added, cc.	Measured mean vol. of erythrocyte (A), cubic microns.	Measured diameter, microns.	Calculated thickness, microns.	Calculated mean erythrocyte volume from measured diameter (C), microns.	Volume-thickness index, A/C.	Hemolysis.
Normal	1	0	86	7.6	1.90	86	1.00	0
	2	1	98	7.4	2.30	79	1.24	0
	3	2	110	7.7	2.35	89	1.24	0
	4	3	129	7.2	3.15	73	1.77	0
	5	4	141	7.3	3.40	76	1.86	+
Mild congenital hemolytic jaundice	1	0	87	7.2	2.20	73	1.19	0
	2	1	99	7.0	2.60	68	1.46	0
	3	2	124	7.0	3.30	68	1.81	0
	4	3	137	6.9	3.50	65	2.11	+
Severe congenital hemolytic jaundice	1	0	72	6.1	2.75	45	1.60	0
	2	1	86	6.1	2.95	45	1.91	0
	3	2	100	6.1	3.40	45	2.22	+

The amount of dilution necessary to produce hemolysis varied with the degree of spherocytosis and so depended directly on the shape of the cell. In the severe case with a high volume-thickness index, and so a marked tendency to a globular form, very little dilution was possible before hemolysis began. The cells in this

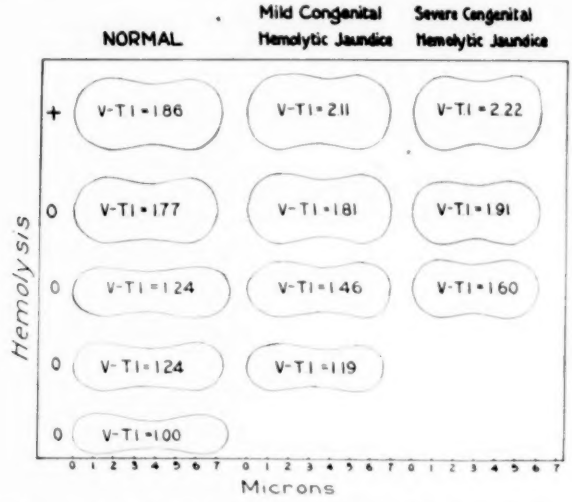

FIG. 4.—Changes in the shape and measurements of the mean erythrocyte in congenital hemolytic jaundice as contrasted with the normal erythrocyte on the addition of varying amounts of distilled water to the plasma (Table 3).

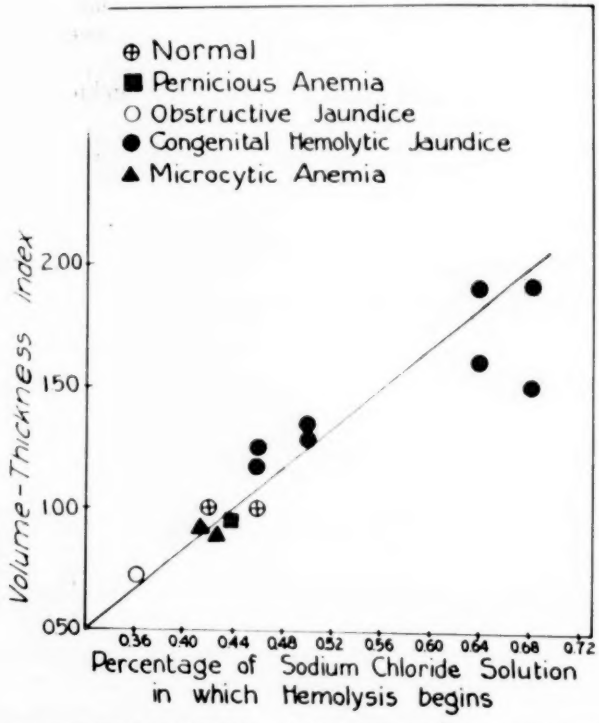

FIG. 5.—The relationship of the point of initial hemolysis of the erythrocytes to the volume-thickness index of the mean erythrocyte.

disease may be regarded as nearer the hemolysis point by reason of their shape.

It is apparent from these results that the point at which hemolysis begins in hypotonic saline solutions should be predictable from the volume-thickness index and likewise the tending to globular form from the minimal resistance. I have charted a group of cases of congenital hemolytic jaundice in Fig. 5, in comparison with obstructive jaundice and other types of anemia. There is a close relationship between the point of initial hemolysis and the volume-thickness index. In obstructive jaundice the diameter of the mean cell is increased (Fig. 1), without change in volume, so the thickness and volume-thickness index are less than normal. In such a blood the resistance is increased. If the diameter and thickness are equally increased as in pernicious anemia or equally decreased as in simple microcytic anemia (Fig. 1), the volume-thickness index and consequently the resistance are normal.

Conclusions. The erythrocytes in congenital hemolytic jaundice constantly exhibit spherocytosis, best shown by the increased volume-thickness index.

The diameter of the red cell in this condition is always less than normal; the volume is variable.

When placed in hypotonic salt solutions, norn erythrocytes become progressively more globular with little cha in diameter as the solution is made more hypotonic.

There is a direct relation between the volume-thi ess index and the fragility of red cells.

In congenital hemolytic jaundice, the erythrocytes have at the beginning one of the shapes through which a normal cell must pass when placed in successive dilutions of hypotonic salt solution, and so may be regarded as nearer the hemolysis point.

The one fundamental variation from normal in congenital hemolytic icterus is the microspherocytosis. The anemia, jaundice, splenomegaly, reticulocytosis and increased fragility are all secondary to the globular form of the erythrocyte.

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THE VALUE OF THE BLOOD SEDIMENTATION TEST IN THE ROUTINE MEDICAL EXAMINATION OF ADOLESCENTS AND IN CERTAIN OF THEIR DISEASES.

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Since the introduction of the blood sedimentation test by Fahraeus[5] in 1918 its value as an index of the presence of a disease process has gradually become more widely appreciated, and its part in the routine examination of patients in gynecologic[6] and tuberculosis[2] clinics become generally accepted, but the employment of this diagnostic aid is not general in routine health examinations. Schattenberg[8] has advocated its use in public health and preventive medicine as an aid in detecting obscure disease and Cutler[3] has emphasized its use in the practice of general medicine. The yearly health examination of school children is certainly a public health enterprise which should be encouraged, but the difficulties which attend such a procedure are obvious; no matter how meticulous and competent the examiner, pathologic conditions may easily be overlooked. In an effort to eliminate such errors, the tuberculin test and Roentgen ray examination of the chest have been added by some health officials to the physical examination. As a possible further diagnostic aid in the yearly health examination of preparatory school boys, we began evaluation of the routine use of the blood sedimentation test in 1932. It was also employed during the course of certain diseases among those boys, to ascertain what changes take place during those illnesses in that age group, and of what significance or value the knowledge of such changes might be.

Method. Beginning in the fall of 1932, each boy presenting himself for his medical examination received a blood sedimentation test. In 1933 about $\frac{2}{3}$ of the examinees were tested both by the Cutler[1] and the Wintrobe[9] method. We have found it convenient and satisfactory to report the readings of these tests at $\frac{1}{2}$ and 1 hour after they were set up; in somewhat less than half the cases, readings were also made at the end of 2 hours and at the end of 18 hours. These examinations were made during the fall term of each school year and the boys were under medical supervision during the remaining months of those years. In general the group might be presumed to be especially healthy since its members were all from homes where proper hygiene and medical supervision had always been available. Our opportunity of observing the boys during subsequent months further justifies the assumption that these boys were normal. Cutler[1] has considered that the normal rates at 1 hour for male adults range between 2 and 8 mm., with the average falling between 3 and 4 mm.; in female adults the range is from 2 to 10 mm., with the average between 5 and 6 mm. Wintrobe[10] has found the range at 1 hour for males and females to be from 0 to 9 mm. and from 0 to 20 mm. respectively, and that 86% of normal males fall in range of 0 to 6.5 mm.

In addition to the tests made on presumably normal boys, other tests were made during certain acute febrile illnesses for the purpose of determining to what degree the sedimentation rate might have been affected. It was also hoped that the test might prove to be of aid in determining the subsidence of the pathologic process in such a disease as bronchopneumonia, in which there is a prolonged convalescence and the time at which normal activity may be resumed is always difficult to determine. The value of this test in following the course of rheumatic fever has been reported by other writers.[4]

RESULTS. In Table 1 and 2 will be found the readings of the blood sedimentation rates we obtained in 685 normal boys ranging in age from 12 to 20 years. It is our experience that the most significant readings are those obtained at ½ hr. and 1 hr., the former serving as a guide to the rapidity with which the blood achieves the latter level.

TABLE 1.—THE BLOOD SEDIMENTATION RATE IN NORMAL ADOLESCENTS. CUTLER METHOD.

Time interval.	½ hr.	1 hr.	2 hrs.	18 hrs.
Range	1–6	1–12	2–20	13–29
Mean	1.5	3.2	7.5	21.5
Median	1	3	7	22
Mode	1	2	6	23
Number of cases	557	557	212	212

(Values for normal adults at 1 hour, Cutler[1]: males range 2–8 mm., average 3–4 mm.; females, range 2–10 mm., average 5–6 mm.)

TABLE 2.—THE BLOOD SEDIMENTATION RATE IN NORMAL ADOLESCENTS. WINTROBE METHOD.

Time interval.	½ hr.	1 hr.	2 hrs.	18 hrs.
Range	1–10	1–20	2–31	16–52
Mean	2.0	4.7	9.7	32
Median	2	3	9	33
Mode	1	2	3	30
Number of cases	200	200	200	200

(Values for normal adults at 1 hour, Wintrobe[10]: males, range 0–9 mm., females, range 0–20 mm.)

Table 3 lists the results obtained by both methods in those individuals whose rates were at the upper limit of normal; and also shows the close parallel of results by the two methods. The examination of those tables indicates that the average normal male adolescent's blood sedimentation rate is about 3 mm. during the first hour by the Cutler technique; and about 4½ mm. by the Wintrobe technique. The normal range for the first hour is from 1 to 12 mm. by the Cutler technique and from 1 to 20 mm. by the Wintrobe technique. Of the individuals 90% had rates of 6 mm. or less in 1 hr. by the Cutler method, and 93% had rates of 10 mm. or less in 1 hr. by the Wintrobe technique. The individuals whose sedimentation rates are listed in Table 3 were carefully followed by the Medical Department but at no time was there any evidence that any of these boys was suffering from an acute or chronic dis-

ease. In these cases, and in any instances in which the sedimentation rate was abnormally accelerated, the hematocrit was determined according to the method suggested by Wintrobe[9] in order to eliminate anemia as a factor.

TABLE 3.—THE BLOOD SEDIMENTATION RATES BY BOTH CUTLER AND WINTROBE TECHNIQUES IN NORMAL INDIVIDUALS WITH UPPER NORMAL RATES AND NO ANEMIA.

Case.	Time interval. Method.	½ hr. C	½ hr. W	1 hr. C	1 hr. W	2 hrs. C	2 hrs. W	18 hrs. C	18 hrs. W
R. H.	....	4	4	9	15	15	27	25	45
K. H.	....	5	7	11	19	15	30	23	47
C. A.	....	6	10	12	20	17	35	26	52
J. R.	....	5	6	11	17	18	29	28	49
E. F.	....	3	7	9	16	16	26	27	50

Brief notes are given below concerning the 4 individuals who were found to have an acceleration in their sedimentation rate and in whom there was evidence of lesions which could account for that condition. In Table 4 will be found the sedimentation rate readings for each of those individuals. In the case of D. B. it may be said that the greatest value of this test is found, for although the lesions were quite extensive, it is not at all difficult to imagine that in a hasty examination they might have been overlooked.

TABLE 4.—THE BLOOD SEDIMENTATION RATES IN INDIVIDUALS IN WHOM PATHOLOGIC PROCESSES WERE PRESENT.

Case.	Time interval. Method.	½ hr. C	½ hr. W	1 hr. C	1 hr. W	2 hrs. C	2 hrs. W	18 hrs. C	18 hrs. W
D. B.[1]	....	13	24	19	43	22	50	25	55
D. H.[2]	....	5	5	10	12	18	30	23	45
R. L.[3]	....	6	..	12	..	..	..	..	..
H. L.[4]	....	8	17	15	40	20	48	25	52

[1] This boy said he felt well at the time of his medical examination; but recent weight loss, cough and lassitude were admitted upon further questioning. His general appearance suggested tuberculosis and careful physical examination and Roentgen ray of the lungs confirmed that impression and explained the accelerated sedimentation rate.

[2] This boy had an appendectomy 4 weeks previously which probably explains the acceleration of the sedimentation rate on that day.

[3] This boy felt well on the day of his medical examination and no abnormalities were noted. The cause of the slight acceleration in sedimentation rate was obvious the following day, however, when he was admitted to the infirmary with cough and fever (Temp. 100). During the course of his bronchopneumonia, the sedimentation rate became further accelerated (Table 7).

[4] The probable explanation of the acceleration in this case was history of a recent severe common cold and subsequent frequent injections of "cold" vaccine as prophylactic measure.

In a number of individuals suffering from moderately severe common colds the sedimentation rate was determined, and a small representative list of readings are given in Table 5. It will be seen that, in general, there was little acceleration in the rate. In 6 cases of mumps (Table 6) the rate was somewhat accelerated in those individuals who had the more severe infection.

TABLE 5.—THE BLOOD SEDIMENTATION RATES IN THE COMMON COLD.

	Time interval.		½ hr.		1 hr.		2 hrs.		18 hrs.	
Case.	Day of disease.	Method.	C	W	C	W	C	W	C	W
C. B.	6	....	4	3	10	20	17	36	24	45
M. D.	3	....	5	4	11	18	19	40	25	50
R. F.	6	....	5	11	8	21	14	33	23	48
R. G.	5	....	7	5	16	23	23	42	27	51
J. M.	4	....	4	11	8	19	..	..	..	..
L. M.	4	....	2	3	5	9	10	18	21	43
N. P.	3	....	3	3	7	11	16	30	26	45
G. P.	5	....	2	3	7	11	15	24	27	45
J. R.	3	....	6	10	12	24	17	37	25	..
W. W.	6	....	3	3	7	9	12	17	22	41

TABLE 6.—THE BLOOD SEDIMENTATION RATES IN MUMPS.

	Time interval.		½ hr.		1 hr.		2 hrs.		18 hrs.	
Case.	Day of disease.	Method.	C	W	C	W	C	W	C	W
R. M.	5	....	5	15	14	31	18	42	25	51
	11	....	6	15	12	25	16	33	25	48
H. M.	2	....	4	6	8	16	17	35	23	43
	8	....	3	8	11	21	17	29	22	46
W. W.	3	....	3	2	7	9	13	20	25	44
G. Y.	4	....	1	1	2	2	6	3	20	25
	9	....	1	1	2	2	5	10	16	25
W. Y.	2	....	5	8	10	19	13	22	22	44
W. Y.*	8	....	9	19	17	37	22	46	26	50
H. H.†	4	....	3	4	10	17	17	34	23	46

* Complicated by orchitis on 6th day; † bilateral orchitis only.

In a prolonged illness such as bronchopneumonia, there is a more satisfactory opportunity of observing the effect of a disease process on the sedimentation rate. In 5 cases of bronchopneumonia in adolescents the sedimentation rates are recorded. It will be seen in Table 7 that there is little increase in the rate at the onset of the disease, but that during the development of the pneumonic process the rate becomes accelerated. It is also obvious that with the onset of convalescence there is a gradual return of the sedimentation rate to normal.

We have also frequently employed this test in helping us to determine whether or not pathologic processes were present in individuals whose past history or general appearance or symptoms suggested chronic disease. In such instances the finding of a normal sedimentation rate has given us greater confidence in the advisability of expectant treatment, and in our attempts to reassure the patient.

Comment. As part of the routine medical examination of 685 preparatory school boys, about 750 blood sedimentation tests have been done either by the method of Cutler or of Wintrobe. We have found that this test gives us further assurance that no obscure pathologic processes have been overlooked. It is true that up to the present time the test has not uncovered unsuspected disease

in many instances, but it is to be remembered that we are dealing with a group whose age and advantages should make them relatively free of illness, and that should only a rare case be found, the use of the test would be justified. The value of the test in such a case as D. B. will be apparent at once to any physician who has examined a relatively large group of boys within a comparatively brief time. In addition to the routine tests which have been reported, we have frequently employed the test when the past history or general appearance of a boy has made us uncertain that there was no disease present; in those instances we have been more confident in our opinion that all was well than we could have been had such a test not been available.

TABLE 7.—THE BLOOD SEDIMENTATION RATES IN BRONCHOPNEUMONIA.

Case.	Day of disease.	W. B. C.	Time interval. Method.	½ hr. C	½ hr. W	1 hr. C	1 hr. W
R. C.	2	7300	.....	3	4	7	11
	4	6900	.....	6	12	13	26
	8	7500	.....	20	30	23	45
	13	7900	.....	19	15	24	38
	22	5900	.....	3	4	9	17
B. D.	3	6500	.....	6	6	13	20
	5	6400	.....	9	24	20	44
	8	7500	.....	6	21	20	34
	15	10300	.....	3	6	9	15
J. W.	1	6100	.....	12	15	20	30
	5	7200	.....	17	20	21	38
	21	....	.....	8	11	12	22
R. L.	1	9200	.....	6	..	12	..
	2	8200	.....	6	..	16	..
	6	9600	.....	12	..	23	..
	10	....	.....	7	..	17	..
C. M.	3	6200	.....	5	6	17	18
	8	9400	.....	14	22	23	45
	18	6200	.....	3	16	11	34

It should be emphasized however, that this test is only a diagnostic aid and in no way can supplant a careful physical examination and other established diagnostic procedures. The desirability of having routine tuberculin tests and chest roentgenograms is in no way affected, for it is generally known that the blood sedimentation rate is often but little influenced in incipient tuberculosis; and it is always to be remembered that this test has real limitations and is not infallible.

The value of the blood sedimentation test in the course of acute febrile illnesses in this age group is not very great, and we can see little benefit in its routine use. In such illnesses as bronchopneumonia we have found this test a definite aid, particularly in those individuals whose cough persists and whose convalescence is slow. In those patients a steady decrease in the sedimentation rate gives one assurance that the trouble is gradually subsiding; or a continued acceleration will compel one to investigate more carefully for some complication. The tables recording the rates in a small number of

adolescents suffering from mumps and common colds, indicate how little the sedimentation rate is affected by minor infections of brief duration.

It would seem that the number of normal boys tested is sufficiently large to allow one to determine tentatively the normal range of the blood sedimentation rate in adolescents, and we have adopted the policy of carefully reëxamining and following up boys whose rate is 10 mm. or more by the Cutler technique in 1 hr. or 15 mm. or more by the Wintrobe method. The sedimentation rates of normal adolescents were found similar to those of normal adults. The question as to which of the two methods is more suitable in group testing is difficult to answer. The Cutler tube is somewhat simpler to fill, and in our experience less subject to error when not carefully cleaned; but the Wintrobe tube has the very definite advantage of permitting a subsequent determination of the hematocrit and the consequent elimination of anemia as a factor in an accelerated rate.

Summary. 1. Blood sedimentation rates in 685 normal adolescents are recorded.

2. The blood sedimentation rates occurring in the common cold, mumps and bronchopneumonia of adolescents are reported.

3. The value of the sedimentation test as a prognostic aid in such prolonged illnesses as bronchopneumonia is commented upon.

4. The desirability of including this diagnostic aid as part of the routine medical examination in a program of preventive medicine is suggested.

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METEOROLOGIC EFFECTS ON THE SEDIMENTATION RATE OF ERYTHROCYTES.

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Since Fahraeus[1] reintroduced the erythrocyte sedimentation test, it has been given importance as a part of the diagnostic armamentarium in many parts of the world, especially in Europe, from

which continent most of the earlier reports as to its uses originated. More recently, however American writers have discussed it with the frequency formerly encountered chiefly abroad. Although a general agreement exists[2] as to the functioning of the test, in that it is commonly conceded that a rapid sedimentation rate indicates an acute infection and a decreasing one connotes improvement, yet many investigators are not in accord with these views. Thus, Pinner[3] and his coworkers showed that there was no correlation between the clinical picture of tuberculosis and the sedimentation rate, and he also noted that there occurred rather wide variations from day to day in "normal" individuals.

That these daily variations should occur and be noted in normal persons appears significant in that it leads one to believe that it is on the basis of such variations that disagreement occurs between various observers who were dealing with certain pathologic conditions, and who neglected to account for variations which might occur independent of any pathology.

The writer feels that, as a result of the observations to be described in this paper, it will be found that the basis of the variations in the sedimentation rate may be explained by the changes that are produced on "normal "or "abnormal" individuals by meteorologic conditions, rather than by the inroads of disease.

Although the exact mechanism of the sedimentation test is not known, many theories have been advanced. (As far as is known) it is now believed that the fibrinogen content of the blood is one of the most important factors.[4] Recently Freeman[5] noted a correlation between the carbon-dioxid content of the venous blood and the settling rate of erythrocytes. Hence there may be one or several yet unknown factors that determine the rate, and we make here no attempt to postulate the cause for the settling. We do believe that variations in the individual rates depend largely on environmental and meteorologic conditions.

During the course of the past 6 years, one of us (W. F. P.)[6] has worked out the detailed physiologic and pathologic changes that are associated with meteorologic alterations, and also has demonstrated the close reflection of the shifting cyclonic fronts in the adaptive mechanism of the mammalian organism. Thus pressor episodes, falling carbon-dioxid and increasing blood pH, localized or general anoxemia, alternates with periods when the diastolic blood pressure falls, the carbon-dioxid content increases, the blood pH decreases, basal metabolism, and oxidation increases. The first phase is termed the ARS phase, and the latter COD phase. The ARS phase coincides with the infall of polar air (but may at times occur at periods of unusually high temperature and humidity). The COD phase usually is coincident with the passage of a tropical front, *i. e.*, with the cyclonic period of low barometric pressure. Not only does this rhythm (ARS and COD phase changes) influence

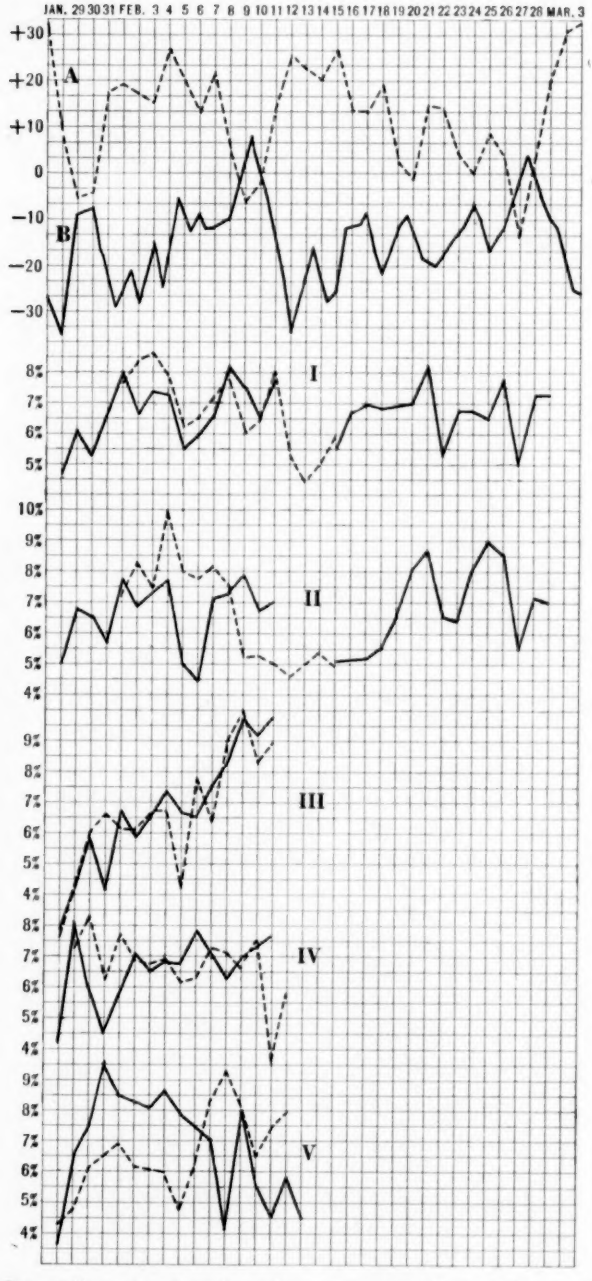
every physiologic process but it is naturally reflected to a greater extent in the individual who is poorly buffered, or in whom some organic dysfunction exists (migraine, epilepsy, eclampsia, psychosis, etc.).

Among the physiologic alterations, changes have been described for the leukocytes, the fibrin, platelets, corpuscular resistance, and so on. Now, if meteorologic conditions are able to bring about changes which may be measured by blood chemistry methods, then these same changes ought to influence the erythrocyte settling rate.

Methods and Observations. — Because of the availability of material, the determinations were made on male patients classified as general paralysis. There were two exceptions to this. Patient 1 had a 4+ blood Wassermann and Kahn test only, and Patient 12 had negative tests for syphilis. The month of February was selected for this study because of the numerous well-marked meteorologic changes which commonly occur during this month. All the determinations were carried out by the writers, under uniform conditions, 1 hour after breakfast (which was always of essentially the same ingredients). The Linzenmeier method was used in all cases in order to report on one method only. In each tube were placed 0.2 cc. of a 2% sodium citrate solution, and 1 0.8 cc. of blood, and these were mixed by inverting the tube 3 times. The time in minutes for the erythrocyte column to reach the 0.18 mark was recorded.

Other methods, namely, the Westergreen and the Cutler, are carried out by measuring the length of the plasma column after the blood has been in the tube for 1 hour. This differs from the Linzenmeier method, but the different procedure in determination has no appreciable effect on the final results. Thus it was stated by Greisheimer[7] that the average sedimentation for the three methods in 1 hour in normal subjects appears to be reasonably concordant, although the differences between the means for the three methods were significant statistically. She also stated that the "dispersals in individual cases about the lines of average relationships although not studied in detail are clearly greater than those ascribable to error inherent in the technic." Thus it was reasoned, that if variations appeared in the Linzenmeier method, these same variations would appear in other methods.

It seems that the results do not depend upon the method used, and hence the disagreements noted among various authors cannot be due to the different methods. Even using the same method, variations occur in normal persons, and although this has been noted by several, no explanation has been advanced. It is quite probable that the issue has been clouded in that the attention has been focused on the effect of diseases, and not upon other factors extraneous to the malady which might independently affect the rate. One might almost sum it up by saying that if a person has a certain disease, then he ought to show a decreased or an increased rate, depending upon the type of the malady.



The sedimentation rate of erythrocytes: An explanation for daily variations.

The period of study extends from January 28, 1934 to March 1, 1934, inclusive and comprises determinations made on 12 patients. In each case 15 determinations were made at daily intervals whenever possible. The patients were so arranged that some one was under observation all the time.

The following table shows the data for the Patients 1, 3, 4, 6, respectively;

TABLE 1.—SEDIMENTATION RATES (IN MINUTES) IN 4 PATIENTS.

Date.	Pt. 1.	Pt. 4.	Date.	Pt. 3.	Pt. 6.
Jan. 28	55	206	Feb. 15	281	194
29	72	291	16	341	196
30	63	271	17	358	193
31	79	237	18	344	208
Feb. 1	95	325	19	345	238
2	78	287	20	357	303
3	89	310	21	418	330
4	87	320	22	262	250
5	65	209	23	342	242
6	71	185	24	341	310
7	75	304	25	332	348
8	98	303	26	394	328
9	9	339	27	240	207
10	74	278	28	375	276
11	94	300	Mar. 1	371	254

In order to obtain similar graphs for each patient, the percentage variation from day to day was determined. Thus for the 15 determinations in Patient 1 a total of 1184 minutes were required. On January 28, the first determination took 55 minutes, or 4.6% of the total 1184 minutes.

In the accompanying graph the percentage variations of the sedimentation rates are compared with the meteorologic conditions present at the time of the determination. Thus the graph lettered "A" shows the daily minimal variations in the temperature, while that lettered "B" indicates the barometric variations. The remaining graphs numbered from I to V were obtained by placing the 12 patients into 5 groups, the patients in each group showing a similar graph. The individual patients are identified according to the character of the line designating the changes:

Graph I. Pt. 1———— Pt. 2 - - - - - Pt. 3————. Graph II. Pt. 4 ———— Pt. 5 - - - - - Pt. 6————. Graph III. Pt. 7———— Pt. 8 - - - - -. Graph IV. Pt. 9———— Pt. 10 - - - - -. Graph V. Pt. 11———— Pt. 12 - - - - -.

In considering the meteorologic conditions present in the period January 27 to March 2, 1934 it is seen that there occurred 9 distinct disturbances. (This is not at all uncommon for February and constitutes one of the reasons that the work was carried out at this time of the year.)

Of the 9 changes, 5 were designated as polar fronts and the remaining 4 as tropical fronts. The changes occurred respectively as follows:

January 28, tropical; January 29, polar; January 31 to February 3, tropical; February 9, polar; February 14, tropical; February 20, polar; February 21, tropical; and February 27, polar.

If the postulate is correct that daily changes in the rate of sedimentation are determined by the response of the organism to weather changes, then definite changes should occur on the dates mentioned above. An examination of the percentage variations in each patient's record discloses that usually definite changes did occur just as would be expected. (In the case of Patients 7 and 8 the effect was cumulative.) Thus, the first 7 determinations were made on January 28 and all have increased rates when compared with the following days. The next day, January 29, the barometer rose and the temperature fell, and all (then 8) of the patients showed relatively slower sedimentation rates. A longer time was required to reach the 0.18 mark.

The changes were rather indefinite on January 30 for of the 8, 3 patients showed a small increased sedimentation rate over the previous day, while 5 showed greater time. The tropical front occurs on the 31st and on that date the time for reaching the 0.18 mark should be shorter. Four out of the 7 showed this change. The same barometric conditions prevailed for the next 3 days. On the first of February, 6 of 9 patients had quicker rates, and on the 2d, 5 were slightly increased, and 5 slightly decreased, the variations being less than 1%. The same conditions existed with practically no change on February 3d.

It appears that the effect is cumulative, because on February 5 all 10 patients had a shorter time to reach the 18 m. mark. The next period of stimulation, or change, occurs on February 9. Therefore changes in the rate ought to occur on February 9 to 10. This is found to have been the case in every particular. This apparent change, occurring at tropical and polar fronts seems to be observable in all cases (it is at these periods when stimulation and changes occur).

Only 2 patients were under observation from February 15 to March 1. The correlation in these instances is self-evident.

This work could have been carried out for an indefinite length of time, but as a correlation was observed and the reasons for it were known, prolonging the observations could have no greater value.

In certain cases, namely Patients 3 and 6, it seems that the rate, whether fast or slow, is determined by the character of the change, whether it is polar or tropical. This is true in general for all cases. However, all that is expected is that the rate should show some change following a cyclonic storm, and that it should tend to the average rate for that individual afterward. Consulting the charts, it is seen that all patients except the two in whom the cumulative effect was observed, tend to group themselves about an average

percentage; thus the average percentage for any case would be 6.6%. If a line is drawn from the 6.6% on the left-hand side of the chart, this is readily seen. In order to clarify and simplify the charts, this line has been omitted.

It must be remembered that the period discussed is but a small fraction of a year, as well as being a part of a season, and that seasonal changes in bodily functions occur. Hence, the accumulative effects may be due to season, and will show an increase in the rate in the following season. Since the interest lies not primarily in seasonal changes, but instead in daily variations in the individual, this work was discontinued at this time.

Conclusions. 1. There occurs wide daily variations in the erythrocyte sedimentation rate, and at times the daily variation is as much as 100%.

2. In general paresis, the rate of settling is slower than in "normal" individuals.

3. There is a correlation between the daily variations of the sedimentation time, and the meteorologic changes.

4. It is believed that these meteorologic changes account for daily variations in the rate of settling.

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YEAST OR VITAMIN B_2 AS "EXTRINSIC FACTOR" IN TREATMENT OF PERNICIOUS ANEMIA.

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According to the studies on the pathogenesis of pernicious anemia published by Castle and associates,[1,2,3] in 1929 and 1930, the antianemic principle is formed through interaction of an intrinsic factor present in normal gastric secretion, but absent in pernicious anemia, and an extrinsic factor present in certain food articles. In 1932, Strauss and Castle[4] tentatively identified the extrinsic

factor with the thermostabile component of the vitamin B complex (B_2). The authors were unable to demonstrate any antianemic effect when 12 gm. of autolyzed yeast was given daily to patients with typical pernicious anemia, whereas there was a strong reticulocyte response when the same dose of yeast or the double dose of autoclaved yeast, as well as an 80% alcoholic extract of the preparation was given after incubation at 37° C. with 150 cc. of normal gastric juice. The yeast preparation used in these experiments was the commercial product "Vegex" which is stated to be "made from fresh washed brewer's yeast by autolysis with salt solution." Exact details of the manufacturing process of this commercial product are not given and are probably not available.

From the results obtained in these experiments Strauss and Castle conclude that the extrinsic factor "may now be defined as a substance closely related to vitamin B_2, if not vitamin B_2 itself." This suggestion of Strauss and Castle has in recent years been much cited in the American literature, though as yet no confirmation of this suggestion has been produced and the hitherto published experiments by other authors go against it.*

Wills and Naish[5] use the white of hen's egg for B_2 preparation (it is stated to contain a good deal of B_2 and no B_1). Daily administration of 40 to 80 "rat doses" of this preparation alone or incubated for 2 hours at 37° C. with 150 cc. of normal gastric juice proved unable to influence the regeneration of red blood cells in typical pernicious anemia. This experiment may, however, be said not to be conclusive, since the patient was not subsequently studied with a combination of gastric juice and extrinsic factor of known activity.

In 1933, Wills,[6] studying tropical macrocytic anemia, a condition in which the intrinsic factor is assumed to be present, presents a series of careful observations on the nature of the hemopoietic factor in "Marmite" (a substance said to be similar to "Vegex"). In these experiments the B_2 content of the yeast preparations used was checked and dosage administered accordingly. Wills found the following preparations inactive in tropical macrocytic anemia: dried distiller's yeast, aqueous extracts of brewer's yeast, the acid clay vitamin B preparation of Jansen and egg white. In sharp contrast to this, maximal or marked reticulocyte response was obtained after ingestion of several different preparations of unflavored "Marmite:" the crude commercial product itself, acid as well as alkalin aqueous extracts and 80% alcoholic extract of "Marmite" (the residue was inactive) and autoclaved "Marmite" (5 hours, 120° C.). From these observations Wills concludes that the extrinsic factor is not identical with vitamin B_2. She consequently turns

* Dr. Castle, to whom this manuscript has been shown, writes that he is fully prepared to relinquish the suggestion that vitamin B_2 is the extrinsic factor and points out the difference between Vegex or Marmite and the preparations used here.
EDITORS.

her attention to the nature of "Marmite" as distinct from other yeast preparations. Regarding the process of manufacture of "Marmite," Wills offers the same data as advanced by Strauss and Castle concerning "Vegex," and, aware of the discrepancy between the negative results obtained with whole yeast and watery yeast extracts and the positive results with "Marmite," she suggests the possibility of the extrinsic factor in "Marmite" being some unknown protein breakdown product in the commercial preparation.

In spite of the evidence cited above, which in our opinion strongly suggests that in the tropical macrocytic condition the exogenous factor is not identical with vitamin B_2, it has been widely assumed that this vitamin plays a rôle as extrinsic factor in true Addisonian pernicious anemia.

In the studies presented in this paper our chief object has been to ascertain the possible rôle of vitamin B_2 as exogenous factor in classical pernicious anemia.

I. MATERIAL. The more important findings in the 8 cases of typical pernicious anemia on which our studies are based are tabulated below:

SURVEY OF CLINICAL AND HEMATOLOGIC FINDINGS IN PATIENTS PRIOR TO TREATMENT WITH YEAST.

Patient No.	1.	2.	3.	4.	5.	6.	7.	8.
Sex	M	M	F	F	M	F	F	M
Age	50	54	51	77	48	56	39	50
Glossitis	+	+	(+)	+	0	+	+	+
Achylia	+	+	+	+	+	+	+	+
Paresthesias	+	0	+	+	0	0	+	+
Myelit. signs	+	+	+	0	0	0	+	0
R.B.C. (millions)	2.0–1.7	1.6	2.2–1.7	2.2–1.5	1.3–1.8	2.0–1.6	3.4–2.7	1.2–1.0
Hemoglobin %	57–52	46	53–40	50–39	30–41	49–44	73–64	35–29
Color index	1.4–1.5	1.4	1.2–1.2	1.1–1.3	1.2–1.1	1.2–1.4	1.1–1.2	1.5–1.5
Plasma color	12	16	7	5	19	7	..	13
Complication	Spondylitis	Diabetes mellit.	Pyuria (B. coli)	Bronchiect.	0	0	Pyuria (B. coli)	Pyuria (B. coli)

Two figures in a column for the same feature indicate the respective values on admission of the patient and at institution of the treatment with yeast alone or with yeast + gastric juice. The plasma color values refer to the findings on admission of the patients.

II. YEAST PREPARATIONS. In the experiments 4 different yeast preparations were used:

1. *Autolyzed Viscid Brewer's Yeast* (*Top Yeast*). Fresh, pressed top yeast containing 25% dry substance is autolyzed for 24 hours at 37° C. In the first experiment the patient was given 12 gm. of this preparation, a brown viscid fluid, daily—similar to Castle's dosage—and 20 gm. a day in the next experiment.

Vitamin B_2 content: 2.5 curative rat doses per 1 gm. (about 30 doses in 12 gm., and 50 doses in 20 gm.).

Vitamin B_1 content: about twice as much per weight unit.

2. *Brewer's Yeast Extract.* Fresh, pressed brewer's yeast containing about 25% dry substance is washed repeatedly, boiling water added and the mixture heated to the boiling point whereafter heating is discontinued. Then filtered through paper and Büchner's funnel and evaporated so that 1 cc. of the extract contains the same amount of dry substance as 2 gm. of the original material. The dosage of this preparation was 40 cc. daily.

Vitamin B_2 content: about 18 curative rat doses per 1 cc. (about 700 doses in 40 cc.).

Vitamin B_1 content: about twice as much.

3. *Distiller's Yeast Extract (Autoclaved for 1 Hour at 120° C. at a Pressure of 2.5 Atmospheres).* Fresh, pressed distiller's yeast with 25% dry substance is submitted to the same procedure as preparation No. 2 and evaporated so that 1 cc. corresponds to 4 gm. dry yeast. After this autoclaving for 1 hour at 120° C. The preparation was given in doses of 20 to 30 cc. daily.

Vitamin B_2 content: about 30 curative rat doses per 1 cc., *i. e.*, 600 to 900 rat doses in 20 to 30 cc.

Vitamin B_1 content: only a trace.

4. *Distiller's Yeast Extract (Autoclaved for 5 Hours at 120° C., pressure of 2.5 Atmospheres).* Same method of preparation as for No. 3, but autoclaved for 5 hours. Vitamin B_2 content: about 10 curative rat doses per 1 cc. Daily dose: 20 to 30 cc., corresponding to about 200 to 300 curative doses. This preparation contains no vitamin B_1.

The preparations were assayed on rats as follows: Young male rats, aged 3 weeks, are kept on a vitamin B-free diet until the weight curve begins to fall. Then the rats are given an addition of the B_1 fraction in sufficient doses (standardized preparation), until the weight curve begins to fall anew; after this the rats are given the yeast preparation which is to be assayed for B_2—daily doses by weight.

One curative rat dose means the amount (by weight) of the assayed yeast preparation that is required as a daily dose in order to give an average weekly weight increase of about 8 gm. per test animal.

III. Experimental Technique. The gastric juice is obtained from fasting normal adults (medical students) by aspiration of the stomach contents after injection of histamin in doses from 0.5 to 1 mg. The amount of normal gastric juice employed in each dose has been, as a rule, the amount which the "donor" was able to produce; so, naturally, it has been subject to some variation. Nearly always, however, the dose of gastric juice has been over 50 cc., and usually between 100 and 200 cc., a quite sufficient amount, according to Castle's findings. As soon as the gastric juice is withdrawn, it is mixed with the measured dose of yeast extract, already heated to 37° C., and the mixture is incubated at 37° C. We have not determined the hydrogen-ion concentration in these mixtures; they have nearly always been slightly acid on Congo paper, and always acid on litmus paper. Thus the reaction was always within the limits for interaction between the "intrinsic factor" and the "extrinsic factor" (Castle, Townsend and Heath[3]) and usually near the hydrogen-ion concentration which is considered optimal for extraction of vitamin B_2.

The incubation time for the mixture of gastric juice and yeast preparation has always been the same throughout the individual experiment; otherwise it has been varied from 1 to 1½ hours up to 24 hours.

The patients were given the mixture in the morning, fasting or a few hours after a light morning meal of tea and toast. In some cases the mixture was given without any addition; most often, however, there was added a little dark beer to camouflage the looks and the taste.

IV. Experiments. Case 1 (Table 1).—It is evident that this patient was regressing rapidly during the first two periods of treat-

ment, for it does not seem reasonable to attach any particular importance to the very slight increase in the reticulocyte value, hemoglobin percentage and red cell count as observed at the transition from the first to the second period.

TABLE 1.—RESULTS OF TREATMENT IN CASE 1.

Days		Retics., %	Hb., %	R.B.C., millions.	Days		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	57	2.0	17		1.2	44	1.8
					18		1.1		
5	Period II	0.9			19		1.0		
6		0.7	52	1.7	20		0.7		
7		0.6			21		0.5	45	1.7
8		0.1	50	1.7	24		0.4	39	1.3
10		0.5			25		0.7		
11		0.5			26		0.8		
12		0.6							
13		0.4	42	1.5	27	Period III	0.6	41	1.4
14		0.6							
15		1.5			45			63	3.5

Period I (from 5th to 15th day): prep. No. 4, 20 cc. daily—no gastric juice.
Period II (from 17th to 26th day): prep. No. 1, 12 gm. daily + normal gastric juice (150 to 280 cc.), incubated for 2 hours at 37° C.
Period III (from 27th day): large doses of active preparation from pig stomach (ventriculin).

Results. B_1-free distiller's yeast extract given in a daily dose containing about 200 effective rat doses of B_2 has no antianemic effect or, at most, only a minimal effect. Twelve grams of autolyzed brewer's yeast daily (about 60 rat doses B_1 and 30 rat doses B_2) incubated for 2 hours at 37° C. with 150 to 280 cc. of normal gastric juice has no antianemic effect.

CASE 2 (Table 2).—This patient fell off so rapidly during the two periods of treatment with yeast and with yeast + gastric juice that it was not considered justifiable to extend the latter period beyond 7 days. In this case there is not even the slightest suggestion of a reticulocyte reaction.

TABLE 2.—RESULTS OF TREATMENT IN CASE 2.

Days		Retics., %	Hb., %	R.B.C., millions.	Days		Retics., %	Hb., %	R.B.C., millions.
1		0.3	46	1.6	12		0.7	36	1.2
2		0.2							
					13	Period II	0.5		
3	Period I	0.2			14		0.4		
5		0.1	47	1.6	15		0.3		
6		0.1			16		0.7	33	1.1
7		0.1			17		0.1		
8		0.1							
9		0.4	35	1.3	19		0.2	31	1.1
10		0.3							
					47		...	68	3.7

Period I (from 3d to 12th day): prep. No. 1, 20 gm. daily—no gastric juice.
Period II (from 13th to 19th day): prep. No. 1, 20 gm. daily + normal gastric juice (80 to 100 cc.), incubated for 2 hours at 37° C.
From 19th day: daily intramuscular injection of 4 cc. of campolon.
From 22d day: daily intramuscular injection of 2 cc. of campolon.
From 35th day: daily ingestion of exhepa corresponding to 500 gm. of fresh liver.

Results. Daily ingestion of 20 gm. of autolyzed brewer's yeast, containing about 100 rat doses of B_1 and 50 rat doses of B_2, has no antianemic effect whatever, regardless of whether the yeast is given alone or after incubation for 2 hours at 37° C. with 80 to 100 cc. of normal gastric juice.

Thus we have not been able to confirm the findings obtained by Strauss and Castle,[4] although we have copied their experimental technique as closely as practicable after their data. Yet is must be admitted—and we want to stress this point—that our yeast preparation was not similar to the preparation used by these authors. As already stated they used "Vegex," a commercial product which is said to have gone through a procedure of prolonged autolysis, including addition of salt. This special process may possibly account for the discrepancy between our results and the results of Strauss and Castle. On the other hand, our findings are quite in accordance with the negative findings obtained by Wills,[6] using ordinary dried yeast and aqueous yeast extracts in the treatment of tropical macrocytic anemia.

From the outcome of these first experiments the idea occurred to us that the divergence might be due to the possibility that our preparation No. 1 did not contain a sufficient amount of vitamin B_2. In the following experiment, therefore, we used a preparation (No. 2) with a greater B_2 content.

TABLE 3.—RESULTS OF TREATMENT IN CASE 3.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	53	2.2	23	. . .	1.6		
5	. . .	0.3	48	2.0	24	. . .	1.2	45	1.7
7	. . .	0.5			26	. . .	1.1		
9	. . .	0.1			27	. . .	0.7		
12	. . .	0.1	49	1.9	28	. . .	0.3		
14	. . .	0.3			29	. . .	0.4		
16	. . .	0.1			31	. . .	0.1		
19	Period II	0.1	40	1.7	42	. . . .	...	43	1.6
20	. . .	0.9			51	. . . .	...	61	2.6
21	Period III	0.7							
22	. . .	1.0	42	1.7					

Period I (first 16 days): no treatment.
Period II (from 17th to 20th day): prep. No. 2, 40 cc. daily—no gastric juice.
Period III (from 21st to 31st day): prep. No. 2, 40 cc. daily + normal gastric juice (80 to 100 cc.), incubated for 1 to 1½ hours at 37° C.
From 42d day: ventriculin in sufficient doses.

CASE 3 (Table 3).—This patient was getting worse at the time treatment was instituted with a daily dose of 40 cc. of preparation No. 2 without addition of gastric juice (on the 17th day). Six to 9 days after this treatment was instituted and after 2 to 5 days of subsequent administration of preparation No. 2 + gastric juice there is a minimal increase in the reticulocyte percentage. It would

hardly be reasonable to attach any particular significance to this slight increase; most likely, it is accidental. But even if not, this increase in the reticulocyte percentage would have to be ascribed to preparation No. 2 alone and not to the combination of this preparation with gastric juice.

Results. Brewer's yeast extract containing about 1400 effective rat doses of vitamin B_1 and 700 rat doses of vitamin B_2 per daily dose has no—or merely a minimal—antianemic effect. After incubation with 80 to 100 cc. normal gastric juice for 1 to $1\frac{1}{2}$ hours at 37° C. the preparation is absolutely ineffective.

After this test we went on to try yeast preparations which contained vitamin B_2 but only very little of B_1 (preparation No. 3) or no B_1 at all (preparation No. 4).

Cases 4, 5 and 6.—These 3 patients were all given distiller's yeast extract autoclaved for 1 hour (preparation No. 3), incubated with normal gastric juice at 37° C. for 1 to $1\frac{1}{2}$ hours. On subsequent treatment with liver preparation or ventriculin all 3 cases had remission; in Case 4, however, the remission was very slow and incomplete, presumably on account of the patient's age and the complicating lung lesion.

Table 4.—Results of Treatment in Case 4.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.	Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	50	2.2	13	3.5	47	
7		0.4	39	1.5	15	4.5	49	2.0
					17	2.2	50	
9	Period II	0.7	40					
11		1.9	42		55	...	67	2.7

Period I (first 7 days): no treatment.
Period II (from 8th to 17th day): prep. No. 3, 20 cc. daily, incubated with 20 cc. of normal gastric juice.
From 17th day: ventriculin, corresponding to 300 to 400 gm. fresh pig stomach daily.

Table 5.—Results of Treatment in Case 5.

Days.		Retics., %	Hb., %	R.B.C., millions	Days.	Retics., %	Hb., %	R.B.C., millions
1	Period I	...	30	1.3	12	0.9		
2		5.0			15	1.9	44	1.6
					16	2.3		
4	Period II	3.0	41	1.8	17	2.1		
5		1.8	40		18	1.6	50	2.0
7		0.9			19	1.5		
8		1.5	40	1.5	21	0.3		
9		1.1						
10		0.4			22	0.5	55	2.1
11		1.0	41	1.6	36	...	65	2.9

Period I (first 3 days): no treatment.
Period II (from 4th to 21st day): prep. No. 3, 20 cc. daily, incubated with 80 to 180 cc. of normal gastric juice.
From 24th day: ventriculin in sufficient doses.

TABLE 6.—RESULTS OF TREATMENT IN CASE 6.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	49	2.0	32		3.5		
4		0.9			33		3.6	45	1.7
7		0.9	47	2.0	34		3.2		
10		0.7			35		3.1		
12		0.3	45	1.9	37		2.7	49	1.9
14		0.4	43	1.6	38		2.6		
					39		3.0		
18	Period II	0.5	44	1.6	40		4.0	55	2.1
19		1.1			41		3.7		
20		0.8			42		1.5		
21		0.2	43	1.5	44		1.4	60	2.4
23		0.7			45		1.4		
24		1.9			46		0.5		
25		1.8			47		0.8	61	2.6
26		1.6	43	1.6	48		0.6		
27		1.7			49		0.5		
28		2.1							
30		3.0	44	1.5	51		0.3	61	2.5
31		2.9			55		...	72	3.0

Period I (first 17 days): no treatment.
Period II (from 18th to 50th day): prep. No. 3, 20 cc. daily, incubated with 60 to 105 cc. of normal gastric juice.
From 51st day: liver extract in sufficient doses.

In these 3 cases (Nos. 4 and 6 were in retrogression when administration of yeast extract and gastric juice was commenced) there appeared during the treatment small, though unmistakable, increases in the reticulocyte percentage, but mostly late in the treatment (Case 4, max. 4.5% after 8 days; Case 5, max. 2.3% after 13 days; Case 6, max. 4% after 23 days). There was at the same time a not inconsiderable increase in the hemoglobin percentage and the red cell count.

In these 3 cases, we think, the possibility of a spontaneous remission cannot be excluded; in Case 5 it is even highly probable that a spontaneous remission was coming on immediately before the treatment was instituted. On the other hand, these remissions might also be said to resemble the remissions observed after small and insufficient doses of liver extract. Whether some part in these remissions is to be attributed to the gastric juice, through its supposed action upon the yeast extract, must be said to be most doubtful, as the produced reactions are not essentially different with regard to magnitude from the minimal reactions observed in the first experiments after administration of yeast extract alone. But, on the other hand, it is not to be denied that there still *is* some difference. In our opinion the *course* of the reticulocyte curves in these experiments suggests that these patients were given a suboptimal dose of antianemic effective principle.

Results. Treatment of 3 patients with a daily dose of 20 cc. of distiller's yeast extract, autoclaved for 1 hour at 120° C. and

incubated for 1 to 1½ hours at 37° C. with 20 to 180 cc. of normal gastric juice, is accompanied in all 3 cases by a slight but distinct reticulocyte reaction which is followed by an increase in the hemoglobin percentage and red cell count. The daily dose of yeast extract used in these cases contains about 600 curative rat doses of vitamin B_2 and only insignificant amounts of B_1.

If one were to maintain the idea that ordinary yeast contains an antianemic factor or a factor that is capable of antianemic effect after it has been exposed to the action of normal gastric juice, the outcome of the tests above would make it necessary also to look for some cause why the obtained remissions—that is, if they actually were "obtained"—have been incomplete (inadequate reticulocyte reactions observed in Cases 4, 5 and 6).

As in our experiments the chief purpose was to ascertain whether any antianemic properties may be attributed to vitamin B_2, the yeast extract employed in Cases 4 to 6 (preparation No. 3) must be said to be suitable, containing considerable amounts of B_2 and very little B_1. According to the works of Castle and his associates,[1,2,3] cited above, the given doses of normal gastric juice must be regarded as sufficient, and the hydrogen-ion concentration of the mixture during the incubation was such as must reasonably be taken to promote a biochemical combination of the "intrinsic factor" in the gastric juice and the presumed "extrinsic factor" in the yeast extract—regardless of whether this "extrinsic factor" were identical with B_2—not suggested very strongly by the results given above—or some other substance present in the yeast extract.

A change in the experimental technique which conceivably might result in production of a larger amount of antianemic principle in the mixture of gastric juice and yeast extract would be a longer period for interaction between the two components. In the last two experiments, therefore, we have used preparation No. 4, which is entirely free from vitamin B_1 and rich in B_2, and we have incubated it with normal gastric juice at 37° C. respectively for 5 to 7 hours (Case 7) and 24 hours (Case 8).

Case 7 (Table 7).—Here the hemoglobin percentage and red cell count were stationary when the treatment commenced, but at that time the red cell count was so high that the reticulocyte response to optimal liver therapy could not be expected to exceed 6 to 7%.

On comparison of the reticulocyte percentages ascertained during the treatment to the values obtained prior to the treatment, this patient, too, may perhaps be said to show an attempt, albeit very feeble, at reticulocyte reaction. The hemoglobin percentage does not increase at all, and the red cell count but very little. The slight reticulocyte increase observed in this case does not differ in magnitude from the preceding reticulocyte reactions after yeast medication alone.

TABLE 7.—RESULTS OF TREATMENT IN CASE 7.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
7	Period I	...	70	3.2	31		1.2		
9		0.1			33		1.5	63	2.8
13		0.4			34		1.8		
16		...	63	2.6	35		1.6		
20		0.3	64	2.7	36		0.8	64	2.6
					37		1.0		
23	Period II	0.2			38		0.9		
24		0.5			40		0.9	63	3.0
26		0.7	65	2.9	41		1.0		
27		0.9							
28		1.0			42		0.6		
29		1.4	65	2.8	43		0.8	62	2.9
30		1.6			65		...	72	3.3

Period I (first 21 days): no treatment.
Period II (from 22d to 41st day): prep. No. 4, 25 cc. daily, incubated with 70 to 140 cc. normal gastric juice.
From 43d day: treatment with ventriculin and, later, with liver extract. The retardation of the remission is due presumably to the complicating pyuria (B. coli).

CASE 8.—This patient was in a rather poor condition when he entered the hospital. To begin with, we had planned a foreperiod of 10 days in which the patient was to have only preparation No. 4, distiller's yeast extract autoclaved for 5 hours. After 5 days, however, in which the general condition of the patient was aggravated, we thought it would not be justified to keep on longer with this medication alone. Besides, in a previous test (Case 1) preparation No. 4 had already proved perfectly ineffective or almost so. We then went on to give the patient a mixture of preparation No. 4 and gastric juice, with a view to the possibility that this mixture might show some effect because the state of the blood in this case left plenty of room for improvement.

TABLE 8.—RESULTS OF TREATMENT IN CASE 8.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1		...	35	1.2	13		0.2		
					14		0.2	28	1.1
2	Period I	0.1			15		0.5		
4		0.6	30	1.0	16		0.6		
5		0.4							
6		0.5	29	1.0	18	Period III	1.1	30	1.3
7		0.2			19		1.7		
					20		2.7		
8	Period II	0.2			21		2.3	28	1.1
9		0.5			22		2.4		
10		0.2							
11		0.2	27	1.0	23		1.9	32	1.1
12		0.3			39		...	52	2.2

Period I (from 2d to 7th day): prep. No. 4, 20 cc. daily—no gastric juice.
Period II (from 8th to 16th day): prep. No. 4, 20 cc. daily, incubated with 100 to 170 cc. normal gastric juice.
Period III (from 17th to 22d day): injection of liver extract in doses which were assumed to be sufficient. Apparently the preparation was inactive. Therefore,
From 23d day: ventriculin in usual doses (typical remission).

Result (Cases 7 and 8).—Administration of vitamin B_1-free distiller's yeast extract (autoclaved for 5 hours at 120° C.), containing 200 to 300 effective rat doses of vitamin B_2 per daily dose, gives no demonstrable antianemic effect after incubation with normal gastric juice in sufficient doses for 5 to 7 hours and 24 hours, respectively. So the longer incubation time has not furthered the production of antianemic active principle.

Conclusions. In accordance with Wills, studying tropical macrocytic anemia, we have to conclude from the results of our tests that the extrinsic factor desired in the treatment of classical pernicious anemia is not identical with the B_2 fraction of the vitamin B complex and, probably, not with any other fraction of this vitamin. On the other hand, these studies suggest that some sorts of yeast (or yeast preparations) contain certain amounts of an antianemic principle, presumably similar to the substance demonstrated in "Vegex" or "Marmite"—that is, if the incomplete remissions observed in some of these cases are not to be regarded as spontaneous. If this active principle be actually present in ordinary yeast, it most likely is preformed or produced through the procedure of autolysis, as it was not practicable with certainty to ascertain any increase in its amount after incubation with normal gastric juice in sufficient doses for periods varying between 1 hour and 24 hours.

Yeast is thus entirely without any antianemic effect under the conditions of this study; or, "at best," it contains only insignificant amounts of antianemic factor.

Summary. Eight patients with typical pernicious anemia have been treated with various yeast preparations, given partly without additions of any kind, partly after incubation with normal gastric juice.

These yeast preparations are assayed by tests on rats as to their contents of vitamins B_1 and B_2. One preparation which contained no B_1 was found to be highly effective against experimental B_2 deficiency in rats.

The extrinsic factor searched for by Castle is not identical with vitamin B_2, nor with B_1, and presumably not with any other fraction of the vitamin B complex.

Yeast appears to be either completely without any antianemic effect, or it possibly contains minimal amounts of antianemic factor.

On addition of normal gastric juice it has not been practicable with any degree of certainty to ascertain an increase in the content of active antianemic principle.

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STUDIES ON THE EFFECT OF NARCOSIS ON THE RATE OF LOCOMOTION OF POLYMORPHONUCLEAR LEUKOCYTES IN VITRO.*†

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The experiments herein reported were designed to answer one phase of the following question: Has general anesthesia any effect on the resistance of the body to infection? The effect of anesthetics on the locomotion of leukocytes is the more immediate phase here considered.

The mobilization of leukocytes is an essential element in cellular immunity. Since mobilization is dependent upon locomotion, it follows that by altering the rate of locomotion of leukocytes anesthetics may thereby alter the cellular reaction to infection. It is obvious that in sufficient concentrations they would narcotize the cell and so inhibit locomotion. This would conceivably affect resistance to infection unfavorably. But what would lower concentrations do? They would possibly increase the motility by decreasing cell viscosity or by some other means. Bond[1] stated that leukocytes of patients under ether narcosis showed increased motility (though he did not report any actual measurements). On the other hand, Pantin[2] found no concentration of narcotic that increased motility of amebæ. Now increased motility in itself might tend to increase resistance to infection. Therefore, I sought any concentration of narcotic that would increase the rate of locomotion

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of polymorphonuclear neutrophils. In the following experiments chloroform was used as the type drug.

Technique. The method employed in these experiments was essentially that of McCutcheon[3] as used by him in studying the normal rate of locomotion of leukocytes. A drop of blood mixed with the chloroform in the ratio of 4 parts of blood to 1 part of chloroform dilution was placed upon a carefully cleaned coverslip. The latter was then gently placed upon a similarly cleaned glass slide so that the drop would spread evenly in all directions. The preparation was then rimmed with vaselin in order to exclude air and placed in a warm box maintained at 37.5° C. Final dilutions of chloroform, ranging from M/64000 to M/125 in geometrical progression constituted the series employed.

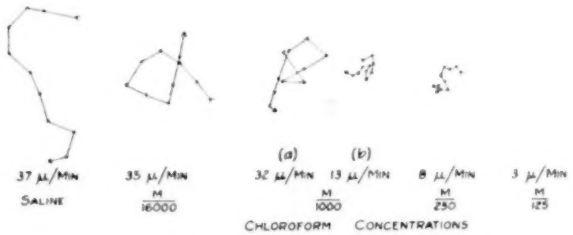

FIG. 1.—Representation of cell movements under various concentrations of chloroform for 10-minute periods.

It is important that these procedures be carried out rapidly and with as little damage to the cells as possible. Therefore, the mixing of the two solutions was accomplished by gently drawing them up into the lumen of a pipette and then gently expelling them. This procedure was repeated several times. To insure as close an approximation to physiological conditions as possible the preparation was allowed to remain in the warm box on the stage of the microscope for at least 45 minutes before observations were

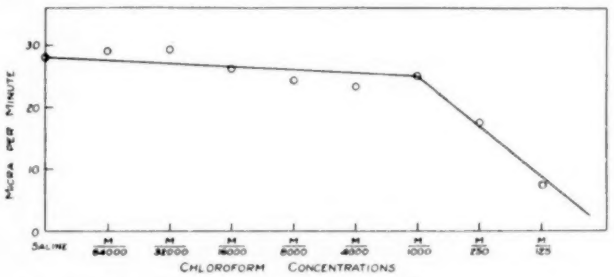

FIG. 2.—Average rate of locomotion at various concentrations.

begun. This was ample time for the cells to recover from the effects of chilling and of the manipulations so that they had once more resumed their normal movements. McCutcheon[3] found that under these conditions the cells maintained normal locomotion for about 7 hours. He also found that after chilling, the cells upon regaining body temperature would resume their normal movements.[4] Therefore, the relative complexity of the above procedures appear justifiable.

The observations were recorded by means of a Zeiss drawing ocular. The cells were observed through the high dry power of the microscope, their images being reflected onto a sheet of paper by means of the drawing ocular. The movements of each cell were observed over a period of 10 minutes, its position at the end of every minute being noted by means of a pencil-point mark in the center of its longest axis. In this manner a series of dots were obtained which when connected represented the movements of the cell over the 10-minute period. Typical results are represented in Fig. 1. Generally, not more than 3 neutrophils appear in the field, and at any one time during the experiments not more than 3 cells were followed. From 10 to 15 cells were observed in any one preparation, and these constituted one experiment.

Control determinations were made throughout the course of the experiments without the addition of chloroform. As before, the blood was diluted in the ratio of 4 parts of blood to 1 of diluent, the latter being normal saline. The blood of the same normal person was used throughout the course of the experiments.

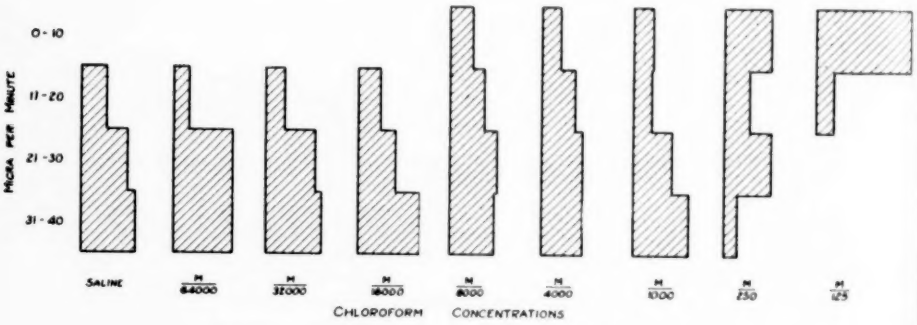

FIG. 3.—Classification of cells in percentage groups.

Results. The cells were classified according to the average rate of locomotion per minute. (Fig. 3.) They were further placed into 4 groups according to their rate over the 1-minute period, *viz.*, those cells moving from 0 to 10 micra per minute constituting the first group; 11 to 20, the second; 21 to 30, the third; and 31 to 40, the fourth. As the distribution of cells in the saline controls and in the 3 lowest concentrations of chloroform is very similar, it is suggested that in these concentrations chloroform had no effect. However, in higher concentrations there is observed an increasing shift toward a slower rate, indicating a definite and progressive effect of the chloroform in decreasing the rate of locomotion. There is no evidence that in any concentration chloroform increases the rate of locomotion.

In the control experiments of the present series an average rate of 28 micra per minute was obtained. (Fig. 2.) McCutcheon found the average rate under normal conditions and a similar technique to be 34 micra per minute. This difference was to be anticipated as the cells were subjected to more manipulations and

the blood was diluted with saline in these experiments. Fig. 2 also shows that there was no significant variance between the effect of low concentrations of chloroform on the cells and under control conditions. A sharp fall in the average rate of locomotion is noted when higher concentrations are reached.

Discussion. The results of these experiments reveal no concentration of chloroform that increases the rate of locomotion of polymorphonuclear leukocytes. Little effect of the narcotic on the cells was observed until concentrations strong enough to narcotize the cells were reached. It is interesting to note the variance in the susceptibility of the different cells to narcosis. This phenomenon is best illustrated at a chloroform concentration of M/250. It is at this concentration that we first note a decided narcotic effect. Nevertheless we still find cells moving between 31 and 40 micra per minute. It is true that the cells were well distributed among the three highest groups in the control experiments, but no cell was found to be moving at a rate greater than 40 micra per minute. Therefore, it appears obvious that all the cells are not affected equally by the chloroform. An adequate explanation of this finding is lacking. Certainly all the cells in the various groups were subjected to the same concentration of the narcotic.

The relation between the concentrations of chloroform used under the conditions of these experiments and those in the blood during surgical anesthesia is an apparent question. Several sets of figures relating to the concentration in the blood during anesthesia are available in the literature. They follow: Nicloux,[5] 0.05% (dog); Tissot,[6] 0.0291 to 0.0464% (dog); Buckmaster and Gardner,[7] 0.026 to 0.05% (cat); Van Dessel,[8] 0.023 to 0.0247% (man).

Van Dessel's figure in man is slightly lower than those occurring in animals. However, both Van Dessel[8] and Alcock[9] state that the differences in the concentrations between the various animals (including man) are not sufficient to vary the conclusions to be drawn from them. From these figures it is seen that during anesthesia the concentration of chloroform in the blood lies somewhere between 0.023% and 0.05%, or in molar concentrations between M/530 and M/240. There is a uniformity of opinion among Nicloux, Tissot, Buckmaster and Gardner, Van Dessel, and Alcock as to the average lethal concentration of chloroform in the blood, namely, slightly higher than a concentration of 0.07% (M/180). However, since Buckmaster and Gardner obtained lethal effects in certain cases at a concentration of 0.045 (M/260) and since the concentration in man is slightly less than that in the animal, it is likely that the actual concentration in the blood during anesthesia is less than M/300. As already pointed out, a definite slowing of the cells occurred at concentrations higher than M/1000. Therefore, it is suggested that the same phenomenon occurs during surgical anesthesia. Since the mobilization of leukocytes is an essential factor

in cellular immunity, it might follow that anesthesia diminishes this phase of the body's resistance to infection.

Summary. 1. A series of experiments have been carried out to study the effects of high and low concentrations of a narcotic (chloroform) on the rate of locomotion of polymorphonuclear leukocytes.

2. Low concentrations of the narcotic have no apparent effect on the cells under the conditions of these experiments, whereas higher concentrations inhibit their motility considerably.

3. The variance in the susceptibility of the cells to narcosis has been noted.

4. The relation between the concentration of chloroform in the blood during surgical anesthesia and those used under the conditions of these experiments has been discussed.

I am indebted to Morton McCutcheon for his help in suggesting and carrying out this problem.

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THE RELATION BETWEEN THE TOTAL RETICULOCYTE PRODUCTION AND THE DEGREE OF BONE MARROW INVOLVEMENT IN PERNICIOUS ANEMIA.*

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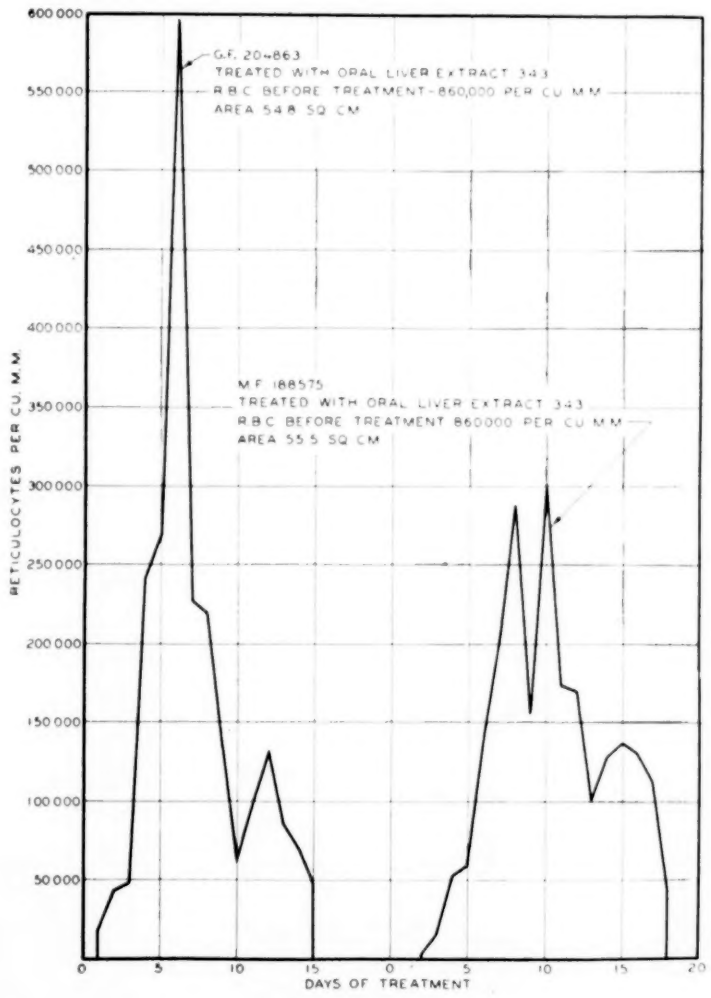
Among the many observations of the effect of liver and stomach therapy upon persons suffering with pernicious anemia, probably the most striking concerns the quantitative relationship between the erythrocyte level at the beginning of treatment and the subsequent increase in the percentage and absolute number of reticulocytes.

The extensive studies of Minot and his associates,[2,3] Riddle,[4] Bethell and Goldhamer,[5] supported by many other observers, clearly demonstrated that the peak of the reticulocyte rise bears an inverse

* Reported to the Central Society for Clinical Research, October 27, 1933.[1]

relation to the number of red blood cells per c.mm. and that when optimal amounts of potent material are administered, the maximum reticulocyte percentage is definite for any given initial red blood cell count below 3,000,000 per c.mm.



FIGS. 1 AND 2.

Patient No. 1. Patient No. 2.

"Reticulocyte response" curves of different shape but the same area. Both patients had the same initial red blood cell count.

The entrance into the circulation of large numbers of reticulocytes is regarded as an indication of excessive bone-marrow activity, the rate of maturation being so rapid that the developing erythro-

cytes are released before they have attained full maturity. In the usual case of pernicious anemia receiving optimal doses of liver or stomach, the duration of the reticulocyte response varies between 10 and 15 days regardless of the level of the red blood cells. However, an individual will be encountered occasionally, who displays a more sustained response, the reticulocyte percentage being ele-

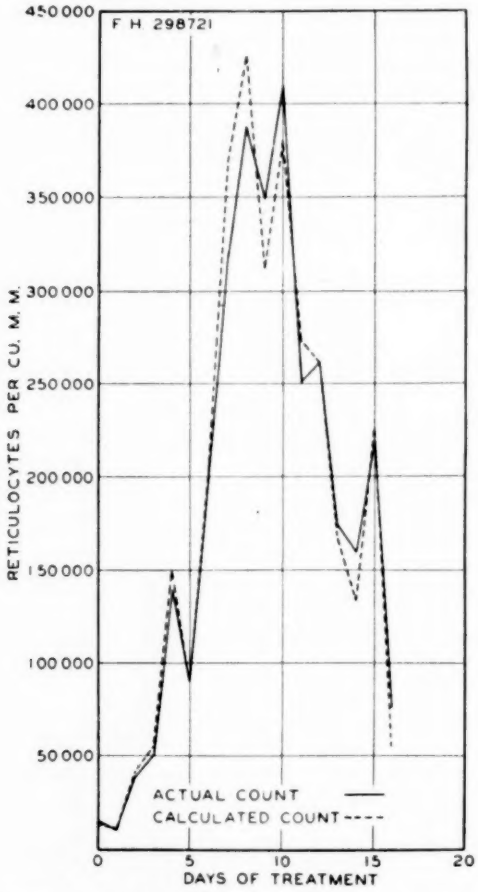


FIG. 3.—Close approximation of curves based on actual blood counts and on counts interpolated from weekly observations.

vated over a period of 20 days or longer. In such a case the maximum percentage is usually appreciably less than would have been expected on the basis of the initial red blood cell count. Furthermore, some individuals exhibit a rapid rise of the reticulocytes to a relatively high level followed by an equally precipitate decline, while others with approximately the same red blood cell count

reach a somewhat lower level and maintain it for 3 or 4 days (Figs. 1 and 2). Such variations in the type of response suggest the importance of determining a measure of the total reticulocyte production regardless of the rate or the maximum value obtained at any given time. The present study was designed to establish, if possible, the relation between the entire reticulocyte response and the initial degree of bone-marrow involvement, as evidenced

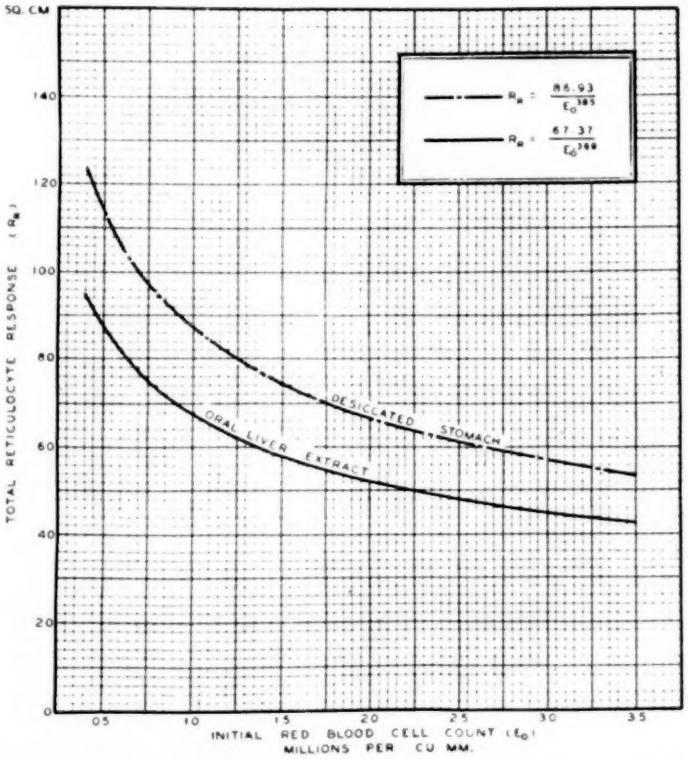


FIG. 4.—Relationship between the total plotted area in square cm. and initial red blood cell count in patients with pernicious anemia receiving liver extract orally and desiccated stomach.

by the red blood cell count at the beginning of treatment in patients who subsequently obtained satisfactory remissions induced by liver extract or desiccated stomach therapy.

Method. The patients, from whom the data under consideration were obtained, were seen at this Institute between 1927 and 1933. The diagnosis of pernicious anemia was established by clinical and laboratory criteria as well as by the subsequent response to specific anti-anemic therapy. Liver extract (343 N. N. R.) or a similar extract was administered by mouth daily in an amount derived from 600 gm. of liver, to 41 patients. Desic-

cated stomach (Ventriculin) was given in a daily dosage of 40 gm. obtained from 265 gm. of fresh stomach tissue to 33 patients. The erythrocyte determinations were made with U. S. Bureau of Standard certified pipettes and hemacytometers. The reticulocyte percentages were estimated by counting the number present in 1000 red blood cells, using cover-glass preparations supravitally stained with brilliant cresyl blue and counter stained with Wright's stain.

It was found that a satisfactory measurement of total reticulocyte production could not be obtained by the use of percentage values. Minot and his collaborators emphasized the value of determining the absolute number of reticulocytes, but as this procedure requires practically daily red blood cell counts and has few advantages in estimating the response to treatment, it has been displaced by the study of the percentage only. For the present purpose it was necessary to have daily red blood cell counts as well as reticulocyte percentages. Since few of the cases studied offered such data a compromise was effected whereby the absolute number of reticulocytes was calculated by multiplying the daily percentage value by the erythrocyte count made on the nearest day. As red blood cell counts were made at least once a week on all patients, the value used in making the calculations was within the limit of error when compared with the actual erythrocyte level. The data given in the following tables and chart, obtained from cases on whom daily red blood cell counts were made, shows the close approximation of the results derived by calculation of the red blood cell level using weekly counts and those secured by utilizing the daily counts (Tables 1 and 2, Fig. 3).

TABLE 1.—METHOD OF CALCULATING CONCENTRATION OF RETICULOCYTES PER C.MM. AND COMPARISON OF VALUES OBTAINED BY CALCULATION AND BY ACTUAL DETERMINATION.

Days.	Red blood cells (in millions per c.mm.).	Reticulocyte percentage.	Absolute No. of reticulocytes calculated from daily red cell counts per c.mm.	Absolute No. of reticulocytes calculated from weekly red cell counts per c.mm.
1	1.60	1.6		
2	1.48	0.8	13,320	14,400 (1.60)
3	1.64	0.6	9,880	9,600 (1.60)
4	1.61	2.6	41,860	38,220 (1.47)
5	1.61	3.4	54,740	49,980 (1.47)
6	1.56	9.6	148,760	141,120 (1.47)
7	1.47	6.1	89,670	89,670 (1.47)
8	1.44	14.3	205,920	200,210 (1.47)
9	1.69	21.8	368,420	320,460 (1.47)
10	1.61	26.4	425,040	388,080 (1.47)
11	1.67	18.7	312,290	349,690 (1.87)
12	1.74	21.9	381,060	409,530 (1.87)
13	2.04	13.4	273,360	250,580 (1.87)
14	1.87	14.0	261,800	261,800 (1.87)
15	1.80	9.3	167,400	173,910 (1.87)
16	1.58	8.5	134,300	158,950 (1.87)
17	1.91	11.8	225,380	220,600 (1.87)
18	1.95	2.8	54,600	76,440 (2.73)
21	2.73			

The values to the right of the last column are those of the erythrocyte count used in making the calculation. This patient received 40 gm. of Ventriculin daily.

The concentration of reticulocytes was determined daily, using the method just described, commencing one day after the beginning of treatment and continuing until the reticulocyte percentage was within 1% of that found on the day treatment was instituted. The values were plotted on standard

graph paper, the ordinate being time represented in days, 0.2 inch (0.504 cm.) representing 1 day; the abscissa being the number of reticulocytes per c.mm., 0.2 inch (.504 cm.) representing 10,000 reticulocytes. Using the base as one side of the curve, the area of each graph was determined with a planimeter.

TABLE 2.—COMPARISON OF THE AREA OCCUPIED BY THE GRAPH OF THE DAILY RETICULOCYTE NUMERICAL CHANGES, PLOTTED ON PAPER, WHEN MADE FROM THE ACTUAL DAILY RED BLOOD CELL COUNTS AND FROM COUNTS INTERPOLATED FROM WEEKLY DETERMINATIONS.

Patient.	Initial red blood cells million per c.mm.	Area on actual count, sq. cm.	Area on calculated count, sq. cm.	Per cent error.
1. M. F.	0.86	40.9	40.7	0.5
2. I. G.	2.04	44.9	45.1	0.4
3. B. H.	1.27	30.1	30.8	2.3
4. F. H.	1.52	40.2	39.3	2.3
5. C. J.	1.91	32.8	32.7	0.3
6. G. J.	0.78	36.0	35.6	1.1
7. W. M.	0.82	92.3	95.1	3.0
8. P. S.	0.64	55.1	56.6	2.7

Maximum error 3.0%. Average error 1.58%. Patients 4 and 5 were treated with Ventriculin; the others received liver extract by mouth.

From the data obtained, formulas were constructed by which a measure of the expected total reticulocyte response can be secured from a knowledge of the initial red blood cell count.

For liver extract by mouth $$R_r = \frac{67.37}{\frac{.369}{Eo}} \text{ sq. cm.}$$

For desiccated stomach $$R_r = \frac{86.93}{\frac{.385}{Eo}} \text{ sq. cm.}$$

In which R_r is the "area of the reticulocyte response" in square centimeters and Eo the initial erythrocyte count (millions per c.mm.).

By the use of these formulas curves were prepared for the "area of the reticulocyte response" similar to those devised by Riddle[4] and by Bethell and Goldhamer[5] for the maximum reticulocyte percentage response in terms of the initial red blood cell level (Fig. 4).

It was found that, while the inverse relationship between the initial erythrocyte concentrations and the total production of reticulocytes is much less marked than in the case of the maximum reticulocyte percentage response, nevertheless, such a relationship does exist, and the total area of the graph is uniformly proportional to the level of the red blood cells at the beginning of treatment.

Summary and Conclusions. In an effort to estimate the comparative quantities of reticulocytes produced during the initiation of a remission in different pernicious anemia patients, the areas circumscribed by the graphs of the "reticulocyte responses" plotted on a standard paper, were measured in square centimeters.

The value so obtained for any patient is an expression of the total reticulocyte response of that patient.

There is a direct relationship between the degree of bone-marrow involvement, as evidenced by the severity of the anemia, and the summation of the reticulocyte response as represented by the area of the graph. Formulas are given which express this relationship.

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THE RELATION OF AMIDOPYRIN AND ALLIED DRUGS TO THE ETIOLOGY OF AGRANULOCYTIC ANGINA.

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A number of authors[1–6] have recently suggested that amidopyrin (pyramidon) and other drugs of similar nature which contain a masked benzene ring may be the cause of the clinical syndrome agranulocytic angina. The evidence presented in support of this hypothesis consists in the fact that one or more drugs of this class have been taken by the patient in considerable quantities for varying periods of time prior to the onset of the disease and supportive evidence is believed to be afforded by the known leukotoxic effect of benzene, together with the fact that the drugs under suspicion contain a modified benzene ring. Madison and Squier[3] found, furthermore, that in 2 of their patients a brief drop in leukocyte count followed the administration of small doses of these drugs after the patients had recovered from their original attack. Hoffman, Butt and Hickey[4] noted that "the only common factor in the 12 cases seen had been the ingestion of amidopyrine." No details are supplied as to the clinical or hematologic pictures in the cases under observation. Madison and Squier[3] also note that all 6 of their cases which continued to take amidopyrin died, whereas in 8 cases in which the drug was prohibited after the onset the mortality was only 15%. The serious implications of these allegations are obvious. A general summary of the situation has recently been presented.[7]

In consideration of the etiology of any condition, several points must be constantly borne in mind. Chance alone may play havoc with our reasoning. To amidopyrin and allied drugs that are taken

in enormous quantities all over the world, it is tempting to attribute the development of this very serious and baffling condition, agranulocytic angina, which has become so prominent within the past few years, coincident with the increasing use of these drugs. Two points, however, have not received sufficient attention. Few authors have given careful consideration to the actual temporal relation of the drug administration to the hematologic picture, both before, during and after the disease, and too little attention has been paid to the fact that under the name of agranulocytic angina there are undoubtedly several entirely different pathologic entities giving rise to similar hematologic and clinical pictures.

The best criteria for the diagnosis of agranulocytic angina that we know of at present are a greatly reduced white blood cell count with almost complete absence of polymorphonuclear cells and a virtually unimpaired red blood cell and platelet count. There should be no bleeding from the mucous membranes or other surfaces, no enlargement of the lymph nodes not readily accounted for by local sepsis and no notable enlargement of the spleen. At the height of the disease there should be few if any immature white blood cells in the peripheral circulation. Neither the fever nor the ulcerations are characteristic. The latter may be absent. The bone-marrow from the vertebra, sternum and femur should show approximately the same picture, namely a cessation of maturation of the white blood cells at the stem-cell stage. It should be said, however, that the pathologic findings are as yet but little known and probably vary considerably from case to case. There should be no other disease present which could logically explain the leukopenia.

Extreme leukopenia with relative or complete absence of the granular white blood cells is not pathognomonic of a single pathologic entity. Such findings do not by any means make the diagnosis of agranulocytic angina. Yet such is often thought to be the case. Extreme leukopenia is seen characteristically in true agranulocytic angina, not rarely in aleukemic leukemia, sometimes in miliary tuberculosis of the bone marrow, Hodgkin's disease, metastatic bone carcinoma and probably a variety of other obscure conditions. It is found in certain patients with overwhelming sepsis. One etiologic agent cannot underly all these conditions and without question their differential diagnosis during life may be extremely difficult or even impossible. Furthermore, it must be remembered that the prodromal symptoms of agranulocytic angina are frequently such as to call for the administration of antipyretics and it is easy to attribute the subsequent development of signs and symptoms to the therapy given, whereas they may in reality be merely a coincidental series of events. This is particularly the case when the drugs have been given for a brief time only and the leukopenia is discovered shortly afterward.

From our cases presenting what we believe to be the classical

picture of agranulocytic angina, 27 cases have been selected for study. The only basis for this selection has been the possession of accurate and unequivocal evidence as to the administration of amidopyrin and allied drugs. No case which might properly be classed as aleukemic leukemia is included. Those cases which came to autopsy presented findings consistent with the diagnosis of agranulocytic angina. Yet the point must, we believe, be stressed that at present the diagnosis of this condition is fraught with much difficulty, and time alone will tell whether from among the cases showing extreme leukopenia may be segregated a true disease entity. Until such a time it is wise to be guarded in our conclusions as to etiology.

From the table it can be seen that to Patients 1 to 7 the suspected drugs were given in considerable quantities rather regularly and for some time prior to the onset of the recognized disease. In these cases the therapy may tentatively be regarded as causative. The reasons for the administration of such therapy were various, but in no case could it be properly said that the drugs were given for the relief of premonitory symptoms of agranulocytic angina. Thus, approximately 26% of the cases studied may possibly be attributed to the administration of the drug, or at least the therapy may be regarded as having an accelerating factor in a patient already subject to the disease in a subclinical form. There is no absolute proof; but the facts are suggestive. Thus far our data support the thesis of those authors who would incriminate the amidopyrin group of drugs. Of these 7 cases, 5 were adequately treated with Pentnucleotide (N. N. R.) and all are now alive and well. Two received no treatment and died. Madison and Squier[3] report that all their patients who continued to take the drug died. Of our 3 patients who continued to take amidopyrin during their attacks, 1 died and 2 recovered. Case 5 continued to take pyramidon regularly and also to have repeated temporary attacks of neutropenia. On withdrawal of all drugs of the amidopyrin series these temporary attacks ceased.

Seven patients (Nos. 8 to 15) were given at various times drugs of the amidopyrin group, and without careful analysis these drugs might easily be incriminated as the cause of the condition. Yet careful scrutiny of the evidence points in the opposite direction. The mortality in this group was 30%. All were treated with Pentnucleotide. It is worth while to examine some of these cases more carefully because, as stated above, without careful scrutiny the amidopyrin might have been incriminated. In Case 9 there was a history of at least 10 major attacks, each occurring at the time of menstruation, with a progressive fall in the average white blood cell level over a year's period. With each attack a lower level was reached. Each recovery was a little less satisfactory. In the midst of her fifth attack she was given 40 grains of pyramidon over a period of 4 days, and during this time her white blood cell count

rose from 800 per c.mm. with no neutrophils to 3700 per c.mm. with 64% neutrophils. During this time she had been under Pentnucleotide therapy. In another attack she was given 30 grains of pyramidon over a period of 3 days and during this time her white blood cell count rose from 1600 per c.mm. with 1% neutrophils to 3300 per c.mm. with 33% neutrophils and continued rapidly to reach a normal level. Thus, relatively large doses of the drug, even at the height of the disease, had no deleterious effect.

FIG. 1.—THE RELATION OF AMIDOPYRIN AND ALLIED DRUGS TO THE ETIOLOGY OF AGRANULOCYTIC ANGINA.

Case No.	Age.	Sex.	No. of attacks.	Lowest W. B. C. per c.mm.	Lowest neutrophil %	Drug taken:			Probable relation to disease.*	Result.
						Before.	During.	After.		
1	88	F	1	500	0	75 days	Yes	0	Causative	Dead
2	55	F	1	300	0	45 days	Yes	0	Causative	Alive
3	30	F	1	3200	0	30 days	0	0	Causative	Dead
4	68	F	1	200	0	30 days	0	0	Causative	Alive
5	55	F	Many	700	0	3 years	Yes	Yes	Causative	Alive
6	66	F	1	1000	0	60 days	0	0	Causative	Alive
7	60	F	1	800	0	14 days	0	0	Causative	Alive
8	50	F	Many	2900	5	Occ.	0	0	0	Alive
9	30	F	10	200	0	0	Yes	0	0	Dead
10	60	M	1	200	0	Occ.	Yes	Yes	0	Alive
11	50	F	Many	400	0	14 days	Yes	Yes	0	Alive
12	50	F	1	2600	2	Irregularly	Yes	Yes	0	Alive
13	38	F	1	300	0	Irregularly	Yes	Yes	0	Alive
14	25	F	3	1200	0	5 mos. before 1st and 2d, none before 3d	0	0	0	Alive
15	50	F	3	500	0	5 days	0	0	0	Dead
16	60	F	9	1000	0	0	0	0	0	Dead
17	50	F	2	1900	3	0	0	0	0	Alive
18	60	M	Many	1000	0	0	0	0	0	Alive
19	50	F	1	600	0	0	0	0	0	Dead
20	65	F	1	450	0	0	0	0	0	Dead
21	63	F	1	1100	0	0	0	0	0	Dead
22	72	F	1	2500	0	0	0	0	0	Alive
23	35	F	1	1000	0	0	0	0	0	Dead
24	37	F	1	1000	0	0	0	0	0	Dead
25	43	F	9	500	0	0	0	0	0	Alive
26	60	M	2	2000	0	0	0	0	0	Alive
27	30	F	1	1000	2	0	0	0	0	Alive

Pentnucleotide was given in varying amounts to all but Cases 1, 3, 19 and 21.

Patient 10 took Peralga rather regularly for a week prior to his only attack. He has, however, taken the drug in larger quantities since that time and, although his blood has been carefully studied,

no changes whatsoever have been noted. Clinically he continues to be well and active. In a similar manner both Patients 11 and 12 took pyramidon and allonal before their attacks, but have also taken it more or less regularly since, without the slightest effect on their white blood cells, as evidenced by repeated examinations. Patient 13 had taken pyramidon irregularly for years before her first attack. During her second attack she was given large doses for 5 days and during this time, while under Pentnucleotide therapy, her white blood cell count rose from 300 per c.mm. with no neutrophils to 1500 with 27% neutrophils. Recovery was rapid and complete. Case 15 was given amytal compound for 4 days prior to her first attack for the alleviation of symptoms which might well have been regarded as prodromal. No such drugs were used before her second attack from which she recovered, nor prior to her third and fulminating seizure in which she died. In a similar manner Patient 14 took moderate quantities (30 grains) of pyramidon each month at the time of her menstruation for 5 months prior to her first attack, and somewhat larger doses (40 grains) each month for 4 months prior to her second attack. Since then, however, she has had no drugs of this type whatsoever and yet 9 months later had a third and equally severe seizure from which she recovered spontaneously.

Twelve patients (Nos. 16 to 27) with similar, if not identical, clinical and hematologic pictures, received no drugs of the amidopyrin series whatsoever either before, during or after their attacks. The mortality in this series was 50%. Ten were treated with Pentnucleotide with a mortality of 40%. Clinically the patients in this category differed in no way from those which took the drugs prior to their illness.

Tentative Conclusions. 1. In 26% of the cases studied the disease followed the administration of amidopyrin or allied drugs. That in these instances the disease may have been actually caused by the therapy is possible, perhaps probable.

2. In another 30% of the cases a critical examination of the evidence shows that in spite of the fact that these drugs were taken in considerable quantities they definitely have no causative relation to the disease.

3. Of these patients, 44% received no drugs of this type whatsoever, yet their clinical and hematologic pictures were similar in every respect.

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AUTOHEMAGGLUTINATION.

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The phenomenon of autohemagglutination has lately received more attention, particularly in regard to blood transfusions. A complete survey of the literature of the subject has been presented by Boxwell and Bigger,[1] who collected 22 cases from the literature up to 1927, and added 2 cases of their own to the list. In the following years, 5 more cases were reported by Rubaschewa,[2] Iwai and Mesai,[3] Le Goff,[4] Manheims and Brunner,[5] and Blenhamou and Nouchy.[6] To this series of 29, I can add 3 additional cases of autohemagglutination, 2 of which were repeatedly transfused without any untoward reaction.

Case Abstracts. Case 1.—L. G., aged 55, female, was admitted to the Israel Zion Hospital suffering from lobar pneumonia of both bases. The patient did not have a crisis, and after 3 weeks of fever she became very anemic and a transfusion was suggested. In attempting to type her blood, autohemagglutination was found and transfusion deemed inadvisable.

Case 2.—F. S., aged 13, female, was admitted to the Trinity Hospital on August 16, 1933, with staphylococcus septicemia and multiple foci of osteomyelitis. The patient remained in the hospital for 6 months and received 5 transfusions. At the time of typing her blood we found that her serum agglutinated her own cells, but upon warming her cells, agglutination occurred only with Type B serum. A Type A donor was used for the transfusions, which were tolerated without any untoward reaction.

Case 3.—A. G., aged 50, female, was admitted to the Israel Zion Hospital with the diagnosis of influenzal pneumonia and diabetes mellitus. Due to the severe secondary anemia a transfusion was decided upon on the 9th day. While typing her blood it was found that the red blood cells were agglutinated by the patient's own serum, but if the slide was warmed to body temperature the agglutination disappeared and the cells became separated. The patient was then given 500 cc. of Type O blood. She suffered no untoward reaction and 5 days later a second transfusion of 500 cc. of Type O blood was given with equal success.

Discussion. Table 1 demonstrates the behavior of serum and red cells of patient L. G., in relation to sera and cells of all 4 blood groups. This serum agglutinated the cells of all 4 groups as well as her own. The patient's red cells were not agglutinated by any other serum and hence the patient classified in Group O.

If patients' serum was diluted 1 to 16, agglutination occurred at room temperature in all groups, whereas the patient's own cells and other cells of Type O were agglutinated up to a dilution of 1 to 32. At body temperature with the serum diluted 1 to 2, agglutination occurred only with cells of Groups AB, A and B, whereas cells of Type O and the patient's own cells did not clump.

Subsequent studies on the relation of autoagglutination to temperature revealed that this phenomenon occurred only at temperatures below 31.5° C. The clumps of the red cells broke up as soon as the temperature was brought above this critical point.

TABLE 1.—AGGLUTINATION BEHAVIOR OF L. G.'S SERUM AND ERYTHROCYTES.

Serum.	Cells.	Agglutination.
Type AB	L.G.	0
Type A	L.G.	0
Type B	L.G.	0
Type O	L.G.	0
L.G.	L.G.	Clumps

Serum.	Cells.	Agglutination.
L.G.	Type AB	Clumps
L.G.	Type A	Clumps
L.G.	Type B	Clumps
L.G.	Type O	Clumps
L.G.	L.G.	Clumps

Serum L. G.

Cells.	20° C.						37° C.	
	1/2	1/4	1/8	1/16	1/32	1/40	1/2	1/16
Type AB	Clumps	Clumps	Clumps	Few	0	0	Clumps	0
Type A	Clumps	Clumps	Clumps	Few	0	0	Clumps	0
Type B	Clumps	Clumps	Clumps	Few	0	0	Clumps	0
Type O	Clumps	Clumps	Clumps	Clumps	Few clumps	0	0	0
L.G.	Clumps	Clumps	Clumps	Clumps	Few clumps	0	0	0

TABLE 2.—AGGLUTINATION BEHAVIOR OF F. S.'S SERUM AND ERYTHROCYTES.

Serum.	Cells.	Agglutination.
Type AB	F.S.	Clumps
Type A	F.S.	0
Type B	F.S.	Clumps
Type O	F.S.	Clumps
F.S.	F.S.	Clumps

Serum.	Cells.	Agglutination.
F.S.	Type AB	Clumps
F.S.	Type A	Clumps
F.S.	Type B	Clumps
F.S.	Type O	Clumps
F.S.	F.S.	Clumps

Serum F. S.

Cells.	20° C.						37° C.	
	1/2	1/4	1/8	1/16	1/32	1/40	1/2	1/16
Type AB	Clumps	Clumps	Clumps	Clumps	Few	0	Clumps	0
Type A	Clumps	Clumps	Clumps	Clumps	Few	0	0	0
Type B	Clumps	Clumps	Clumps	Clumps	Few	0	Clumps	0
Type O	Clumps	Clumps	Clumps	Clumps	0	0	0	0
F.S.	Clumps	Clumps	Clumps	Clumps	Few	0	0	0

Similar studies with the blood cells and sera of Cases 2 and 3 are presented in Table 2 and Table 3. The findings are identical in all 3 cases, with critical temperature at 30° C. in Case 2 and 30.5 in Case 3. Case 2 belonged to Type A, whereas Case 3 was a Type O like the first case.

TABLE 3.—AGGLUTINATION BEHAVIOR OF A. G.'S SERUM AND ERYTHROCYTES.

Serum.	Cells.	Agglutination.
Type AB	A.G.	0
Type A	A.G.	0
Type B	A.G.	0
Type O	A.G.	0
A.G.	A.G.	Clumps

Serum.	Cells.	Agglutination.
A.G.	Type AB	Clumps
A.G.	Type A	Clumps
A.G.	Type B	Clumps
A.G.	Type O	Clumps
A.G.	A.G.	Clumps

Serum A. G.

Cells.	20° C.						37° C.	
	1/2	1/4	1/8	1/16	1/32	1/40	1/2	1/16
Type AB	Clumps	Clumps	Clumps	Clumps	0	0	Clumps	0
Type A	Clumps	Clumps	Clumps	Clumps	0	0	Clumps	0
Type B	Clumps	Clumps	Clumps	Clumps	0	0	Clumps	0
Type O	Clumps	Clumps	Clumps	Clumps	Few	0	0	0
A.G.	Clumps	Clumps	Clumps	Clumps	Few	0	0	0

While we did not dare to transfuse Case 1, we decided to resort to transfusion as a life-saving procedure on Cases 2 and 3, in spite of the abnormal behavior of their blood. All precautions were taken to forestall the occurrence of autoagglutination in the patients, incidental to a lowering of their body temperature. Twenty minutes prior to the performance of the transfusion, an electric baker was applied to their chests and extremities. The arm was wrapped in an electric hot pad and kept there during the entire procedure. Case 2 received 300 cc. of blood at her first transfusion and tolerated this without any untoward reaction. Case 3 received 500 cc. of blood and subsequently other transfusions of also 500 cc., which were equally well tolerated.

These experiences seem to prove that transfusions are not more dangerous to patients showing autohemagglutination than to other persons. The additional warming of the patient's body is perhaps not absolutely necessary, but adds an additional margin of safety.

The blood of Case 3, examined several weeks later, at a time when her temperature had returned to normal, did not show autoagglutination at room temperature any more. The phenomenon,

however, could be elicited by placing the serum and red cells in the ice box for 5 minutes. At room temperature the cell clumps broke up again and agglutination disappeared. In all 3 cases, similarly to most previous observations, autoagglutination occurred in the course of a febrile infectious condition.

Two patients suffered with pneumonia and the third with osteomyelitis due to staphylococcus infection. Only 1 of the 3 patients (Case 3) had a slight degree of jaundice. Anemia of a severe secondary type was present in all 3 cases. The spleen was enlarged in Case 1.

The relative rarity of autoagglutination and its coincidence with severe infection, anemia and affections of liver or spleen is again emphasized by these 3 observations. It was claimed recently by Rubaschewa[2] that autoagglutination occurred also in perfectly healthy people but was usually not detected in the course of ordinary blood counts, which are done with diluted blood and, therefore, reveal only instances of autoagglutination if the titer of the serum is at least 1 to 200. While this objection is pertinent, autoagglutination still appears to be rare, if this phenomenon was observed only 3 times in the course of typing and matching with undiluted blood in a series of approximately 2000 transfusions which I have performed during the past 7 years.

Summary. Three cases are reported in which autoagglutination of the red blood cells occurred at room temperature and disappeared at body temperature.

The phenomenon is due to the presence of agglutinins in the serum which produce clumping of red blood cells of all 4 blood groups at temperature below a critical point. This point is between 30° and 31.5° C.

Two of the cases reported belong to Group O and 1 to Group A.

All 3 cases were suffering with a febrile infectious condition. Reëxamination in 1 case, after recovery of the patient, showed diminution of the agglutinizing power of the serum to an extent that the clumping of the red cells occurred only in the ice box, but not any longer at room temperature.

Two of the 3 patients received blood transfusions 5 and 2 times respectively, without any untoward reaction.

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ESTIMATION OF CARDIAC TRANSVERSE DIAMETER IN CHILDREN AND COMPARISON WITH CARDIAC AREA.

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The desirability of expressing cardiac enlargement in mathematical terms has led to the use of various methods of measuring cardiac shadows by means of the Roentgen ray, either in orthodiagrams or in films. Of the various measures two of the most useful have been cardiac area and transverse diameter, each compared with some standard of normal for those measures. The normal standards have been derived from height, age, weight, transverse diameter of the thorax, and various other measures. P. C. Hodges and Eyster[1] derived regression equations for calculating normal cardiac areas in adults from height, weight, and age, and F. J. Hodges and Eyster[2] derived similar equations for the prediction of normal transverse diameter. Literature with regard to methods is cited in these papers.

P. C. Hodges and the writers have studied a group of normal children and in another paper[3] have presented the equation for prediction of cardiac area which appeared most useful in the examination of children. We are indebted to Dr. Hodges for the privilege of further study of this material. The study on children was undertaken because the formula of P. C. Hodges and Eyster derived from adults was found to be unsatisfactory in predicting the normal frontal plane area in children. It will be shown that the relative usefulness of area and transverse diameter in making normal predictions as well as the formulas themselves is different in children. It is the purpose of the present paper to present equations for the prediction of transverse diameter and to evaluate as far as possible the merits of the two measures of heart size as applied to children.

Sources of Data. The subjects of the study were normal children living at the Mooseheart City of Childhood,* Mooseheart, Illinois, aged 2.9 to 18.8 years and of divers builds. Teleroentgenograms were made with a target-film distance of 72 inches and with exposure times ranging from a half second upward. Orthodiagrams were made also, but because of the fact that they were impracticable in the youngest children the measurements of the films were used in the calculations. Careful physical examinations were done on the day of the Roentgen ray examination, and the height,

* The study was made possible through the coöperation of the administration of Mooseheart and of the Mooseheart Laboratory for Child Research, under the direction of Dr. M. L. Reymert.

weight, and sitting height were measured at the same time. Ages were obtained from the records of the institution and verified by the statements of the children. After rejection of all subjects with definite or suspicious evidence of cardiac disease, and of films that were technically unsatisfactory, the series comprised 85 boys and 84 girls.

Areas and diameters were measured on film tracings and the results corrected for distortion due to divergence. To obtain the correction factors the anteroposterior chest diameter was measured on 5 children of a wide range of size and build and the distance from the chest wall to the film as it lay in the cassette holder was measured. The anteroposterior diameters ranged from 9 to 15 cm.; the distance from chest to film was uniformly 1.7 cm. The assumption was made on the basis of lateral chest films from these children that the central plane of the heart and presumably the major part giving rise to the borders of its shadow lay at about one-third the distance from the anterior to the posterior chest wall. This observation corresponds to that of Bardeen[4] on adults. The object-film distance was estimated on this assumption, and, the target-film distance being uniformly 182.5 cm., the target-object distance was obtained. The correction factor could thus be calculated by the formula,

$$\text{Factor} = \frac{182.5 - (\frac{1}{3}\text{ A. P. Diam.} + 1.7)}{182.5}$$

This fraction is squared for application to area. The correction factors estimated for area lay between .92 and .95; for diameter between .96 and .98. In applying the factors to areas .930 was used for children over 10 years of age, and .945 for children under 10; in applying to diameters .97 was used throughout.

Work now in progress on adults, with an apparatus in which the film is at a greater distance from the chest wall, and with subjects in whom the anteroposterior chest diameters are greater, indicates a possible advantage to the calculation of a correction factor from the anteroposterior chest diameter of each individual. Anteroposterior diameters were not measured in this series, but in view of the small range of the correction factors in 5 subjects it is likely that no substantial error has been introduced.

It should be noted, also, that a correction for distortion due to divergence does not imply any assumptions with regard to other sources of difference between orthodiagrams, slow films, and rapid films. These observations refer only to the slow film, although we feel it likely that they will also prove applicable to the orthodiagram.

An explanation of the symbols used in tables and equations is given in Table 1.

TABLE 1.—NOTATION.

A—Age in years.
H—Height in cm.
Si—Sitting height in cm.
W—Weight in kg.
F—Frontal plane area from film in sq. cm., corrected for divergence.
$\overline{F}$—Predicted frontal plane area in sq. cm.
D—Transverse diameter in cm., corrected for divergence.
$\overline{D}$—Predicted transverse diameter in cm.
M—Mean.
σ—Standard deviation in the units of measurement of the variable to which it applies.
R—Correlation coefficient.
S—Standard error of estimate in the units of measurement of the variable to which it applies.

Statistical Analysis. Accurate definitions of statistical terms and details of the principles of statistical analysis are not within the scope of this paper, but some explanation may be of assistance to those unfamiliar with statistical methods.

The *mean* is the arithmetical average. The *standard deviation* is a measure of dispersion of measures about their mean. It is the square root of the average of squares of deviations of the measures from the mean. *Correlation coefficients*, as used in this paper, are numbers between zero and one, when positive correlation is present, representing the degree of relationship of one series of measures with one (*zero order correlation coefficient*) or more (*multiple correlation coefficient*) other series of measures on the same group of individuals. When one series of measures tends to decrease as the others increase the correlation is said to be negative and the coefficient is between zero and minus one. A correlation coefficient of zero denotes a complete lack of relationship and signifies that one measure is of no value in predicting the other. A correlation coefficient of one or minus one denotes complete mutual interdependence. A *regression equation* is an equation used to apply correlation coefficients to the prediction of one set of measures, the *dependent variable*, from one or more other sets of measures, the *independent variable* or variables, due allowance being made for intercorrelation between the independent variables when more than one is used. The *standard error of estimate*, while calculated in actual practice from correlation coefficients and standard deviations, represe[illegible]the square root of the average of the squares of all differences betwe[illegible]d and predicted values of the dependent variable.

Graphs of the combinations in pairs of the variables, cardiac area, transverse diameter, height, sitting height, age and weight revealed relationships sufficient to straight lines to justify the application of the Pearson [illegible]ment formula and the development of regression equations. A determinant method was utilized for the multiple correlations; the methods are described in standard statistical textbooks such as that of Kelley.[5]

TABLE 2.—MEANS, STANDARD DEVIATIONS, AND ZERO ORDER CORRELATION COEFFICIENTS.

	M	σ	Zero order correlation coefficients					
			D	F	H	Si	A	W
D	9.89	1.178	1.000					
F	77.36	21.02	.....	1.000				
H	139.2	22.28	.769	.887	1.000			
Si	74.81	10.07	.....	.899	.966	1.000		
A	11.06	4.04	.724	.860	.917	.919	1.000	
W	36.94	14.98	.810	.923	.935	.950	.908	1.000

Zero order correlation coefficients, means, and standard deviations are listed in Table 2. Cardiac area correlates better with the other measures than does transverse diameter. Both measures correlate better with weight than with height, and with height than with age. The correlations of the independent variables one with another indicate that either height or sitting height may be used, but that there is little likelihood of value in using both in the same formula. Age correlates quite well with both height and weight. Similar quantities were calculated for the sexes separately, but because the advantage in accuracy was slight when multiple correlations and regression equations were developed, these figures are dropped from further consideration.

Eleven equations were developed for prediction of cardiac area and four for prediction of transverse diameter. Sitting height offered a slight advantage over height in some formulas, insufficient in our opinion to justify the greater inconvenience of measurement, as the difference in the multiple correlation coefficient varied from .000 to .003. The formulas derived from some combinations of variables are listed in Table 3. With each formula is given the multiple correlation coefficient and the standard error of estimate; standard errors of the coefficients are indicated directly beneath the coefficients. Accuracy of prediction is indicated by the standard errors of estimate and by the correlation coefficients; the probability of general usefulness of measures is indicated by the standard errors of their coefficients.

TABLE 3.—EQUATIONS FOR THE PREDICTION OF CARDIAC AREA AND TRANSVERSE DIAMETER.

(The standard error of each of the coefficients is indicated beneath the coefficient.)

Equation.	R	S
$\overline{F} = \underset{.213}{.405}\ Si + \underset{.397}{.300}\ A + \underset{.135}{.970}\ W + 7.9$	.929	7.77
$\overline{F} = \underset{.078}{.180}\ H + \underset{.116}{1.045}\ W + 13.7$	.925	7.97
$\overline{D} = \underset{.0075}{.00851}\ H - \underset{.0352}{.0369}\ A + \underset{.0107}{.0615}\ W + 6.8$	.817	.680
$\overline{D} = \underset{.00677}{.00490}\ H + \underset{.0101}{.0569}\ W + 7.1$	.811	.689
$\overline{D} = .0637\ W + 7.5$	.810	.690

The probable error of estimate, sometimes used in statistical work, is a measure which may be used instead of the standard error; it is .67449 times the standard error, and designates the range within which the best half of the predictions may be expected to fall in a normal distribution of errors. In a group of measures with such a distribution of errors, half of the observed measures will vary from the predicted measure by an amount exceeding the probable error of estimate. Since positive and negative errors are presumably equally frequent, half of these, or one-fourth of the entire group, will exceed the predicted measure by more than the probable error of estimate. This fact does not justify the conclusion drawn in some other papers on the Roentgen ray measurement of heart size that three-fourths of the hearts that exceed the predicted heart size by more than the probable error of estimate are pathologically enlarged. While the conclusion may be drawn properly that the probability of this class among normal hearts is one-fourth, the conclusion that the probability of normality of hearts in this

class is also one-fourth is in serious error when the data are derived entirely from normal subjects.

In the prediction of cardiac area there is a slight advantage in correlation coefficient and standard error of estimate in using age as one of the variables; the standard error of the coefficient of age, however, is in excess of the coefficient itself. In a series of this size it is considered unlikely that a measure will be of value when applied to other populations if the standard error of its coefficient is in excess of half the coefficient. For this reason it is possible to drop age as a variable and thus make the formula more conveniently applicable without any sacrifice of accuracy. In the formulas for the prediction of transverse diameter the use of height increases the correlation by .001 and the use of height and age increases the correlation by .007 above the correlation with weight alone. The standard errors of the coefficients of age and height are large, however, in comparison with the coefficients, hence these formulas may not be expected to predict transverse diameters generally appreciably better than the formula involving weight alone. The formulas chosen as statistically satisfactory, therefore, are:

$$\overline{F} = .180\ H + 1.045\ W + 13.7$$
$$\overline{D} = .0637\ W + 7.5$$

Comparison of Results. In comparing the accuracy with which each of these cardiac measures may be predicted, the standard errors form a satisfactory means of comparison. It is obvious, however, that an error of, say 5%, is of greater significance in a group of measures ranging from 90% to 110% of a mean than in a group ranging from 70% to 130% of its mean. In other words, the significance of an error is distinctly dependent on the degree of dispersion of the series of measures. Since the measure of dispersion used in the calculation is the standard deviation, a true comparison of the standard errors of estimate requires that they be expressed in terms of standard deviations of the quantities to which they apply. The quantities, standard error of estimate divided by standard deviation, are the coefficients of alienation, usually designated by the letter K (Fig. 1). Included with this graph is a comparison of the coefficients of alienation derived from the figures of P. C. Hodges and Eyster and of F. J. Hodges and Eyster* for adults.

To determine the relative accuracy of prediction for different portions of our series we have determined the difference between predicted and observed cardiac area, and the difference between predicted and observed transverse diameter in each subject. The absolute value of the individual errors has been averaged by height

* The probable error of estimate given by F. J. Hodges and Eyster is smaller than would be indicated from their data; it appears that they failed to extract the square root of the term $1-R^2$ in the formula for its calculation. Apparently this error did not affect the rest of their figures. We have calculated the standard error of estimate from their multiple correlation coefficient.

classes, and the results are expressed in a graph (Fig. 2). In this graph, for proper comparison, the errors in each measure are expressed as fractions of the standard deviation of that measure. The greater accuracy of prediction of cardiac area appears constant throughout the group.

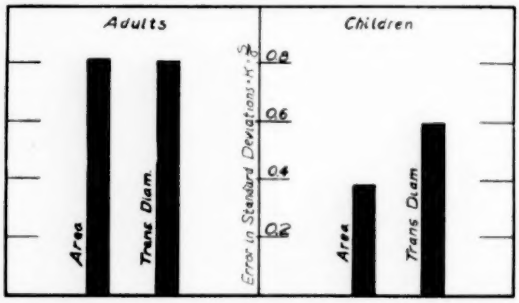

FIG. 1.—Standard errors of estimate in terms of standard deviations (coefficients of alienation).

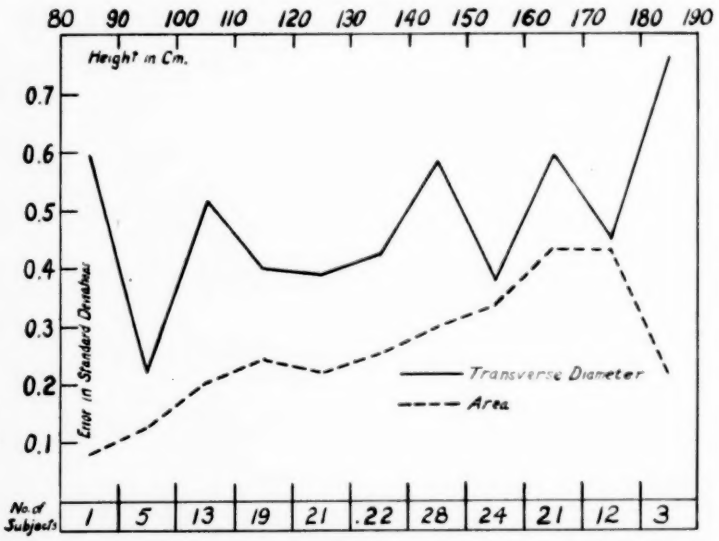

FIG. 2.—Average error in predictions of cardiac area and transverse diameter by height classes, expressed as fractions of their respective standard deviations.

The papers referred to previously indicate that the cardiac area and the transverse diameter may be predicted in adults with practically equal accuracy. The correlation coefficients are .579 and .588, and the standard errors of estimate are .814 and .810 standard deviations respectively. In children, on the other hand,

the correlation coefficients are .925 and .810, and the standard errors .379 and .587 standard deviations respectively. The complete explanation for the difference between adults and children in this respect is not evident. The difficulty in locating the lower border of the heart, one of the greatest sources of error in estimating cardiac area, is considerably less in our experience in children than in adults; this may be responsible in part for relatively better measurement of area. It is also worthy of note that the negative correlation between height and transverse diameter present in adults is not present in our series of children. When age and height are both used with weight there is some negative correlation with age, subject, however, to sufficient error that it may be peculiar to this series. It is possible that the relationship between height and age, on the one hand, and transverse diameter, on the other, undergoes considerable change from one end of our series to the other, if the influence of weight be held constant.

With regard to the apparently greater accuracy of predictions of each of the cardiac measures in children than in adults mathematical deductions may be misleading. While the "efficiency" of the prediction formula $(1-K)$ is considerably greater in each case in children than in adults, it must be remembered that the efficiency of the formula denotes the amount of improvement of the prediction over a random guess for each individual at the mean. In a group such as children in whom all the bodily measurements vary through a wider range in proportion to their mean values, the prediction may be expected to move relatively farther from the means than in adults. For this reason the statistical measures of efficiency used here are not mathematically comparable in groups covering widely different ranges of measures, although they are a reliable guide in comparing different sets of measures in similar or identical groups. It will be noted that our comparisons on smaller groups than the entire series are based on actual observed differences between observed and predicted measures.

The ultimate answer to the question of which is the better method of estimating heart size does not depend entirely on the accuracy with which each of the quantities can be predicted. Since measures of heart size are used in practice for the separation of normal from enlarged hearts, the value of a method depends in practice on how well it separates hearts that appear to be normal from those in which there is other reason to believe that the heart is enlarged. This test has not been applied, so far, to our formulas. Eyster[6] has applied it to several methods of measuring the heart in adults and found that, in spite of approximately equal accuracy of prediction in the normal, the cardiac area method separated the normal from the abnormal somewhat better than any method involving transverse diameter which he used. While such a test of these formulas is desirable, it would appear unlikely that transverse diameters

predicted with so much less accuracy in the normal, as appears from these figures, could separate normals from abnormals with greater accuracy than cardiac areas determinations.

Summary. 1. The relations of cardiac area and cardiac transverse diameter, as measured by the Roentgen ray, to sitting height, height, weight, and age have been studied in a group of normal children.

2. Both measures correlate better in children with weight than with height or age.

3. An equation is presented for the prediction of normal transverse diameter and a comparison is made with cardiac area prediction formulas previously published from the same material.

4. Cardiac area in normal children can be predicted with greater accuracy than transverse diameter by any of the measures used. The advantage of cardiac area over transverse diameter as a measure of normal heart size appears to be greater in children than in adults.

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THE Q WAVE IN THE ELECTROCARDIOGRAM.

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Since 1930, when Pardee,[1] made a critical study of 43 cases showing a significant Q wave in the third lead of the electrocardiogram, other papers have appeared further analyzing records showing this wave.[2–8]

The Q_3 wave rarely appears in normal individuals. In a series of 277 normal cases, Pardee,[1] found a Q_3 wave in only 2 records, and Edeiken and Wolferth,[3] found a Q_3 wave in only 1 record out of 826 electrocardiograms, and in this 1 case it was later found that the individual had a cardiac lesion. From the electrocardiograms of the 1103 normal individuals thus examined for a Q_3 wave, it was found, therefore, in only 2 cases or an incidence of only 0.18%.

Factors other than heart disease, however, have been shown to cause in some cases a Q_3 wave. Krumbhaar and Jenks,[9] observed a Q_3 as a common finding in the electrocardiograms of infants 2 to 12 months of age. Any condition which will elevate the diaphragm

and rotate the heart to the left may result at times in a Q_3 wave.[1,3,5] The short, thick-set, hypersthenic type of chest with a high diaphragm, or ascites or gas distending the abdomen,[5] and thus elevating the diaphragm, may at times cause a Q_3 wave. Pregnancy,[1,3,10] especially in the later months, in some cases probably acts in a similar manner, for all cases which showed a Q_3 during pregnancy did not show it when electrocardiographed after delivery. Respiration,[1,5] likewise has been shown to effect the size of the Q_3 wave, becoming larger with expiration and the resulting elevation of the diaphragm, and smaller with inspiration. France[6] stresses the fact that coronary disease often occurs in the elderly, obese, thick-set individual, so that lateral displacement of the heart must be considered, in this type, before placing too much significance in a Q_3 wave which might be present.

In going through our files we found 125 electrocardiograms showing a Q_3 wave which conformed to the criteria for a significant Q_3 wave as laid down by Pardee.[1] Cases included in this study are those in which:

1. The Q_3 wave was at least 25% of the greatest R in any lead; (2), the initial downward deflection (Q) was followed by an upright deflection (R) without an S wave; (3) records showing a Q_3 wave but where the R_3 was greater than the R_2 and all so-called M or W complexes were omitted.

Of the 125 cases found some were referred for an electrocardiogram only, so that complete histories were not available in these cases. The histories of 108 cases, however, were complete and satisfactory for a critical study, and an analysis of these cases is given in Table 1.

TABLE 1.—AN ANALYSIS OF 108 CASES OF SIGNIFICANT Q_3 WAVE RECORDS.

	No.	%
Total cases	108	
Angina pectoris	54	50
Hypertension	14	13
Arteriosclerotic heart disease not above	22	20
Preceding coronary thrombosis	4	3.7
Other forms of heart disease:		
Rheumatic heart disease	2	1.8
Thyrotoxicosis	1	0.9
Unclassified group	11	10

Nine cases of angina pectoris had hypertension making a total of 23 cases having hypertension.

Twenty cases gave a history of a previous coronary thrombosis, 16 of these also having either angina pectoris or hypertension and so being classified in the latter groups.

Fifty-four (50%) had angina pectoris. In this group are included all cases of typical clinical angina pectoris, characterized by attacks of substernal pain brought on by exertion and relieved by nitrites. Of these cases 9 also had hypertension but were included in the group.

Fourteen (13%) had hypertension which includes all cases not having the anginal syndrome, but whose blood pressure was elevated above 150 systolic and 100 diastolic.

Twenty-two (20%) are classified under arteriosclerotic heart disease, not having angina pectoris or hypertension. These cases showed cardiac disease characterized by arteriosclerosis, and dyspnea on exertion, or signs of congestive heart failure. Many of these cases undoubtedly represent coronary disease which could not be classified under the angina pectoris or hypertension group.

Four (3.7%) gave a history of a typical preceding attack of coronary thrombosis, diagnosed as such, but which was not preceded or followed by any signs of heart disease except for the presence of a moderate degree of arteriosclerosis. In all, 20 of our cases (18%) gave a preceding history of a coronary thrombosis which occurred anywhere up to a year previous to the time our record was taken. Of these 16 had either angina pectoris or hypertension and so are classified under the latter groups.

There were 2 cases of rheumatic heart disease and 1 of thyrotoxicosis with cardiac involvement.

Eleven cases (10%) were placed in an unclassified group. Of these 3 showed vague heart symptoms which could not be definitely classified, while the remaining 8 cases had no heart symptoms. Of these 8 cases there was 1 of pernicious anemia, 1 of empyema of the gall bladder, and 2 of intestinal stasis. Of the 11 cases there were 6 of obesity in the short, heavy-set type, and it may be that the Q_3 wave was caused by an elevated diaphragm in some of these cases. Two others suffered from a severe degree of flatulence, which has also been shown to cause a Q_3 wave at times.

In order to determine if possible the significance of a record showing a Q_3 wave alone, from records which exhibited other abnormalities besides the Q_3 wave, our cases were divided into two groups, termed normal and abnormal respectively and are seen in Table 2.

TABLE 2.—AN ANALYSIS OF NORMAL AND ABNORMAL $Q\,R\,S\,T$ WITH A Q_3.

	Normal cases.	Group %	Abnormal cases.	Group %
Angina pectoris	18	38	36	60
Hypertension	2	5	12	20
Previous coronary thrombosis	0	0	4	6
Arteriosclerotic heart disease not above	15	32	7	11
Rheumatic heart disease	2	5	0	
Thyrotoxicosis	1	2	0	
Unclassified group	9	19	2	3
Total	47		61	
Total cases having hypertension	4		19	
Total cases having had a previous coronary thrombosis	0		20	

The normal group includes those records which showed a normal record except for the presence of a Q_3 wave, and includes those

records with a negative T in the third lead. Under the abnormal classification are included those cases which in addition to the Q_3 wave showed slurring of the $Q\ R\ S$ in more than one lead, or T wave negativity in Leads I, I and II, I, II and III, or II and III. There were 47 cases classified under the normal group and 61 cases under the abnormal group.

Angina pectoris was present in 60% of the abnormal group, while present in 38% of the normal group. France,[6] in a similar analysis of 32 cases in each group found a higher percentage of angina pectoris in the abnormal group (72%) and a much smaller percentage (9%) in the normal group.

The incidence of hypertension is also higher in the abnormal group, while those cases which could not be classified as having any coronary disease are more frequently seen in the normal group.

From these findings it would appear that the incidence of coronary disease is higher in patients whose electrocardiograms show other abnormalities besides a Q_3 wave, and that in the absence of other abnormalities a record which shows a Q_3 alone is more often found in those who have no coronary disease.

Pardee[1] stresses the significance of the relative size of the Q_3 wave as compared to the greatest R in any lead, stating that when the Q_3 was 50% or more of the maximal excursion, 73% of his cases had angina pectoris. Pardee says that the large Q_3 is associated with any pathologic changes that involve coronary narrowing and it would seem that the larger the Q in relation to the $Q\ R\ S$, the closer the relationship.

Ziskin[5] states that in his series when a Q appeared which was 50% or more of the greatest R, 65% had coronary disease.

Because of the great variation in the size of the R waves in different records, and in order to see whether it was the ratio of the Q_3 to the greatest R, or the actual size of the Q_3 itself, irrespective of the size of the R, Tables 3 and 4 were prepared.

TABLE 3.—SIGNIFICANCE OF THE RATIO OF THE Q_3 TO THE GREATEST R.

	Ratio of the Q_3 to the greatest R expressed in percentage.							
	No. Cases 25–35	No. Cases 36–45	No. Cases 46–55	No. Cases 56–65	No. Cases 66–75	No. Cases 76–85	No. Cases 86–100	No. Cases over 100
Total cases	22	26	17	13	14	4	8	4
Angina pectoris	10–45	10–38	6–35	7–54	8–57	3–75	6–75	4
Hypertension	1–5	5–19	2–12	1–8	3–21	1–25	1–12	0
Arteriosclerotic heart disease not above	5–23	4–15	9–53	2–15	1–7	0	1–12	0
Rheumatic heart disease	2–9	0	0	0	0	0	0	0
Thyrotoxicosis	0	1–4	0	0	0	0	0	0
Unclassified group	3–14	5–19	0	2–15	1–7	0	0	0
Preceding coronary thrombosis	1–5	1–4	0	1–8	1–7	0	0	0
Total hypertension	2	7	3	2	4	2	3	0
Total coronary thrombosis	1	5	1	6	3	1	3	0

It will be seen from these two tables that the actual size of the Q_3 wave alone is of more significance than is its ratio to the greatest

R, and that the deeper the Q, the greater the significance. While the percentage of the ratio of the Q to the greatest R increases as the incidence of coronary disease increases, it does not do so in as proportionate a manner as it does in Table 4, where the size alone of the Q wave is taken.

TABLE 4.—SIGNIFICANCE OF THE DEPTH OF THE Q_3 WAVE.

	Size or depth of Q_3 in millimeters.			
	To 3 mm. No. %	3 to 5 mm. No. %	5 to 7 mm. No. %	Over 7 mm. No. %
Total cases	28	44	20	16
Angina pectoris	10–36	19–43	13–65	12–75
Hypertension	1–4	4–9	5–25	4–25
Arteriosclerotic heart disease not above	12–43	10–23	0	0
Thyrotoxicosis	0	1–2	0	0
Unclassified group	3–11	7–16	1–5	0
Preceding coronary thrombosis	1–4	2–5	1–5	0
Total hypertension	1	9	5	8
Total coronary thrombosis	5	8	2	5

From Table 4 it would seem that a record which shows a Q_3 of 5 mm. or over in depth probably represents a record from a serious case of heart disease. Only 1 case exhibiting no cardiac symptoms was seen in records with a Q_3 of 5 or more mm. in depth. Cases of previous coronary thrombosis were about equally divided among different Q_3 sizes and ratios, and were unexpectedly seen with greater frequency in the records with smaller Q_3 waves.

In many electrocardiograms exhibiting a Q_3 wave, a Q_2 wave was noted also, and because of the relative frequency with which this wave was seen, a study of these cases was made. Cases which exhibited a Q_3 wave, which followed Pardee's criteria and also a Q_2 wave, were selected. The Q_2 was chosen if it was a well-defined wave and was not followed by an S_2 wave greater than the Q_2. No restrictions were made on the depth of the Q_2 or its relationship in size to the R as was done in the selection of Q_3 records. In 8 cases an S_2 wave was seen which was larger than the Q_2 and these records were eliminated from this study. In 1 case a small S_2 was seen which was smaller than the Q_2 and was included in our group of Q_2 and Q_3 cases.

Of the 108 cases 34 showed a significant Q_2 as well as a Q_3, this representing a total of 31% of the Q_3 group (Table 5).

TABLE 5.—AN ANALYSIS OF 34 CASES SHOWING A Q_2 AND Q_3 WAVE.

	No.	%
Angina pectoris	23	67
Hypertension	6	18
Arteriosclerotic heart disease not above	5	15
Total cases	34	100

A total of 9 cases had hypertension (3 of these also had angina pectoris).
A total of 8 cases had a preceding coronary thrombosis.

It will be seen that 23 cases (67%) were classified as having angina pectoris, while hypertension and the arteriosclerotic group made up the other 33% of records. Eight cases (23%) gave a history of a previous coronary thrombosis.

Fenichel and Kugell[2] record 6 cases in which a large Q_2 was seen and in 2 of these the Q_2 was even larger than the Q_3, while in another the Q_1 was the largest. Myocardial infarction with septal involvement was found in all 7 cases. They state that while this data is insufficient to draw any conclusions, it would seem that a large Q_2 or Q_1, normally infrequent might have the same significance as a large Q_3.

It would appear from our 34 cases and Fenichel and Kugell's 7 cases, which came to autopsy, that the presence of a Q_2 and Q_3 is of more significance than is the presence of a Q_3 alone. In our group the high percentage of angina pectoris and the absence of other forms of non-coronary disease is, we feel, significant.

Pardee[11] in 1920 described a case of coronary thrombosis in which a Q_3 wave appeared and since then it has been described by others.[12,13,14]

Levine's series[12] of 82 cases of coronary thrombosis show a Q_3 wave in 40% of cases. Parkinson and Bedford,[13] noted a Q_3 wave in 9 cases of coronary thrombosis. Edeiken and Wolferth,[3] illustrate a record of Q_3 developing after occlusion which was not present before.

Figure 1 represents a case of coronary thrombosis which has been followed by frequent electrocardiograms. Following the attack, the electrocardiogram was typical of coronary thrombosis, showing a high take-off of the S–T segment, in Leads II and III, and a Q_2 and Q_3 wave. As healing took place, the S–T segment took off nearer the isoelectric line, and the T wave negativity first increased, and then decreased. The Q_3, which in the first record after the attack was quite large, decreased in size and then later increased. On July 17, 1929 the record shows besides the Q_2 and Q_3 (which are as prominent as before), T wave negativity in Leads II and III, but nothing characteristic nor diagnostic of the coronary thrombosis which had occurred only 2 months before.

Figure 2 represents the same case as in Fig. 1, almost a year after the acute attack. The T wave in Lead II has now become diphasic, and in Lead III almost isoelectric. The Q_2 and Q_3 remain, however, and are even greater in depth than in the records taken previously.

We believe that a large Q_3, and especially a record showing a Q_2 and Q_3 wave, is very significant, and believe with Fenichel and Kugell,[2] that the Q wave is often the only remaining graphic evidence in the electrocardiogram of the remains of a pathologic process which at one time was acute. We believe that many cases showing a Q_3 and many more showing a Q_2 and Q_3 are cases which at

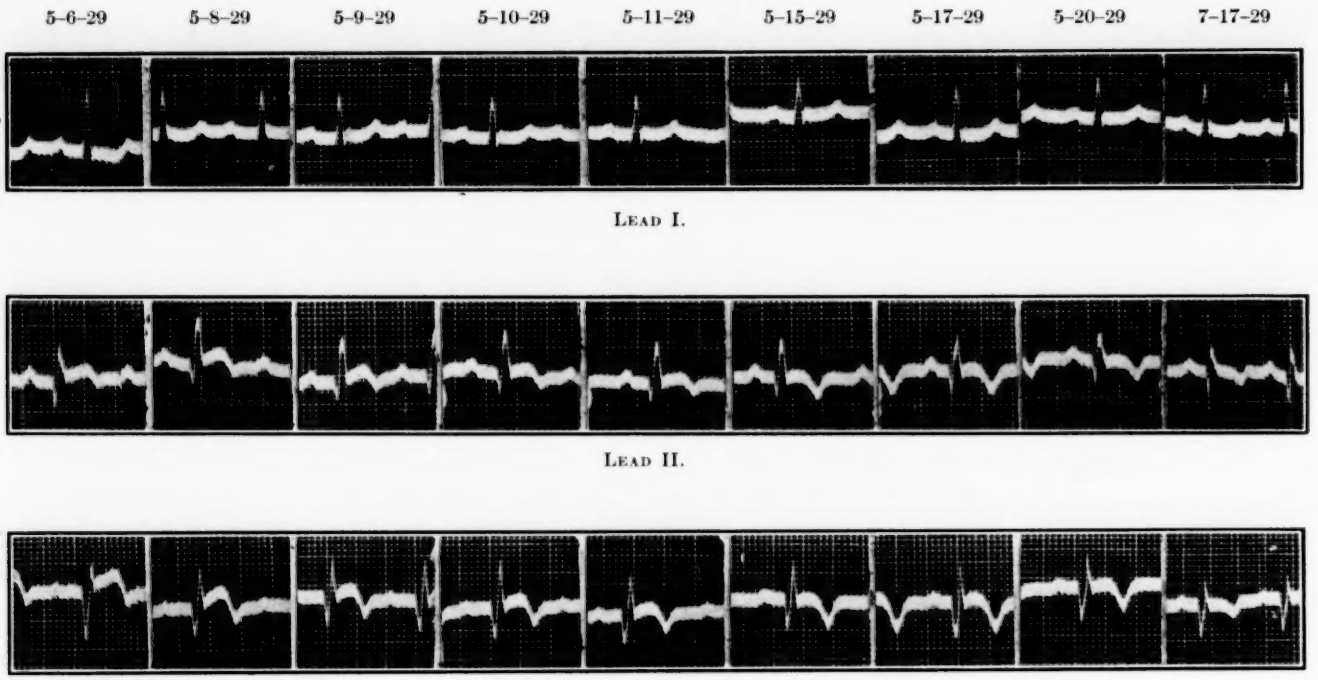

Fig. 1.—Coronary thrombosis. The acute attack occurred 48 hours before the first record taken on May 6, 1929. Note the persistence of the deep Q_2 and Q_3 waves throughout the series.

some previous time suffered from an acute severe myocardial ischemia, and went possibly diagnosed either as a severe attack of angina or went unsuspected.

While the presence of a Q_2 and Q_3 wave is more uncommon than a Q_3 wave alone, we believe that when it is seen, its significance is much greater than when a Q_3 wave alone is noted.

Two of our cases of Q_2 and Q_3, which were normal records in every other respect, gave definite histories of a preceding coronary thrombosis.

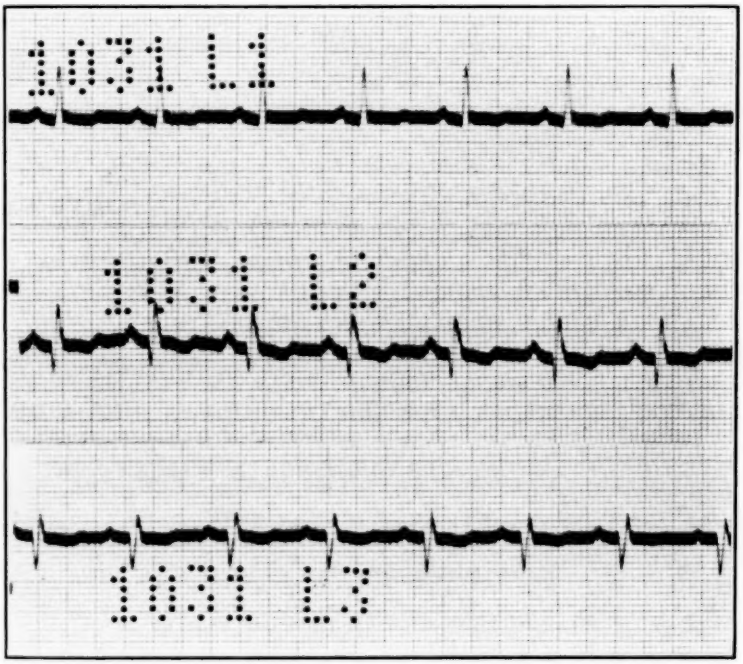

FIG. 2.—From the same case as Fig. 1, taken April 23, 1930 almost 1 year after the acute attack of coronary thrombosis. Note that the Q_2 and Q_3 waves still persist, and are even larger than in the records taken soon after the acute attack, while other signs of coronary thrombosis have disappeared from the record.

Summary and Conclusions. Of 108 cases showing a significant Q_3 wave, angina pectoris was found in 50% and hypertension and arteriosclerotic disease of the heart in 33%.

An electrocardiogram which shows in addition to the Q_3 wave, other abnormal changes, is seen more frequently in coronary disease, although coronary disease is seen frequently enough in the electrocardiograms showing nothing abnormal (except for the Q_3 wave) to be significant.

The depth of the Q wave alone is of more significance than is its ratio to the greatest R, and Q waves of more than 5 mm. in depth were found to be very significant.

A Q_2 and Q_3 wave, when present in the same record, is of more significance than is the presence of a Q_3 wave alone, and we believe that many cases showing a Q_2 and Q_3 wave represent cases of a previous coronary thrombosis in which the Q waves are the only remaining graphic sign of heart damage.

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AORTIC STENOSIS OF INFLAMMATORY ORIGIN WITH A DIFFERENTIAL STUDY OF THE ACQUIRED OR CONGENITAL ORIGIN OF A BICUSPID AORTIC VALVE.*

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Lesions of the aortic cusps offering varying degrees of obstruction to the outflowing blood have been, in our experience, a frequent finding; those alterations of less severe degree characterized by thickening with only a moderate degree of calcification at the roots of the semilunar cusps being much more commonly encountered than the advanced stenoses.

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Pathologically, the distorted aortic valves can usually be classified within one of the following etiologic groups:

1. Of infectious origin, including all cases with "rheumatic" type of pathology, and healed bacterial endocarditis.
2. Arteriosclerotic or degenerative lesions without previous inflammation.
3. Congenitally defective cusps with subsequent calcification (Fig. 1).

FIG. 1.—Congenital bicuspid aortic valve—aortic stenosis—white male, aged 52. There are two valve cusps and two normal commissures. No raphé within the cusp sinuses. Note uninterrupted swing of free edge of valves. The combined cusp, particularly its free margin, shows extensive calcium deposit.

The age at which the lesion is discovered is not always important for pathologic differentiation. Mönckeberg[1] pointed out that the degenerative process might appear within the aortic ring and annulus fibrosus after the age of 35, almost as a physiologic process. He was of the opinion that the amount of calcium deposited varied with individual predisposition, and that the lesion was often well advanced relatively early in life. These lesions being productive in character, deformities associated with concomitant ulceration usually fall within the other two categories of the above classification. With healing and advanced calcification it often becomes increasingly difficult to decide from gross examination whether we are dealing with the healed stage of an originally inflammatory process or with a defective valve of the bicuspid variety with subsequent calcification (Fig. 2).

The criteria formulated by Sir William Osler[2] for the gross identification of the bicuspid valve of congenital origin are exceedingly important and in the majority of cases can still be applied. In difficult cases the chief basis for distinction between the bicuspid valve of congenital or inflammatory origin is the relation of the origin of the fibers of the annulus fibrosus to the aortic elastic media at the ridge or raphé dividing the conjoint valve. Using serial sections stained for elastic and connective tissue, Lewis and Grant[3] have shown that the congenital raphé is merely an abortive attempt to form a commissure in which the normal arrangement of the aortic layers is deformed but not altered, and that unlike the

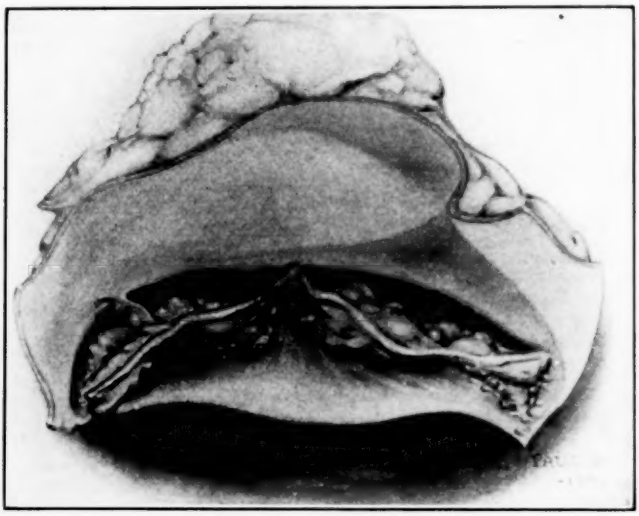

FIG. 2.—Inflammatory (bicuspid) aortic valve showing fused commissure, calcification with aortic stenosis—white male, aged 48. The anterior cusp is divided by a ridge which may be either a fused commissure or a congenital raphé. Such a case of doubtful etiologic nature can be identified by serial section through the questionable ridge.

findings at a normal commissure the relations at the raphé are similar to those found in the center of a normal cusp. However, the fused commissure of old inflammatory origin may present a ridge so shortened and deformed, apparently with two valve cusps of such equal size, that naked eye distinction between such a lesion and a calcified congenital bicuspid valve cannot be made. A case of such a nature occurred in our practice and the study of this specimen, encouraged by Dr. Maude E. Abbott, initiated the present work.

Material and Methods. Nine cases of true congenital bicuspid valves, all except 2 showing a raphé within the sinus, had been

encountered at the Bellevue Hospital morgue during a 2-year period of observation among approximately 5000 autopsies seen through the courtesy of the Office of the Chief Medical Examiner and the Bellevue Hospital Pathological Department. Certain cases of advanced aortic stenosis could not be satisfactorily identified in the gross as to etiology and we undertook the histologic study of this group of specimens. The uncertain cases most often proved to be of inflammatory origin after serial sections through the questionable ridge.

The aortic valves in 12 significant cases were selected for study and differentiation. In those of doubtful nature serial sections, stained for elastic and connective tissue, according to the method of Lewis and Grant,[3] were cut either transversely or sagittally through the ridge or raphé dividing the conjoint cusp. A normal valve and commissure and a typical congenital raphé were similarly sectioned for comparison with the pathologic material. The appearance of the valves in the selected cases varied from healthy bicuspid leaflets, with and without a subdividing raphé, to bicuspid valves extensively calcified. From their gross appearance 2 of the cases of aortic stenosis appeared to be calcified congenital bicuspid valves, in one of which there were associated cardiovascular anomalies. A patent ductus arteriosus and coarctation of the aorta suggested that the deformed and calcified valve was a congenitally bicuspid one, but on microscopic examination both cases proved to be bicuspid valves of inflammatory origin. In another specimen, with subacute bacterial endocarditis, serial transverse sections through a low ridge, whose gross appearance was unquestionably that of a congenital raphé within a bicuspid valve showed the normal relationship of the aortic layers imperfectly reversed.

Discussion. In none of our cases of true congenital bicuspid aortic valves did we encounter variation in the number of pulmonary valve cusps or interventricular septal defects. Dr. Maude E. Abbott[4] has also emphasized the opinion that a congenitally bicuspid aortic valve has in most instances a different developmental etiology than a similar deformity of the pulmonic valve.

The presence of associated cardiovascular anomalies of certain varieties, particularly coarctation of the aorta and patent ductus arteriosus, are considered as important evidence for the congenital (bicuspid) origin of a deformed aortic valve of doubtful nature.[3,4] Our own case, at first considered a congenital bicuspid valve because of the presence of anomalies, subsequently, on section through the decalcified ridge, showed the typical arrangement of layers as found at a normal commissure. The case of bicuspid aortic valves with bacterial endocarditis conformed in its gross characteristics with a typical congenital defect; the imperfect reversal of layers on microscopic examination of the raphé cannot alter the impression of the congenital nature of this bicuspid valve.

Paget[5] seems to have been the first to recognize the susceptibility of this type of valve to subsequent thickening or to infection. Many of his bicuspid valves were unknowingly of inflammatory origin. Peacock[6] reported numerous findings of two aortic cusps but also, erroneously included cases of undoubted inflammatory etiology. Osler,[2] Garrod[7] and Abbott[8] have been among the important contributors in calling attention to the frequency with which these anomalous valves become the seat of calcific deposits or of infective endocarditis.

Conclusions. By the method described by Lewis and Grant it was possible to differentiate a congenital raphé or a fused commissure ridge in aortic valves with advanced calcification and stenosis.

The presence of associated cardiovascular anomalies, coarctation of the aorta and patent ductus arteriosus, cannot be taken as presumptive evidence for a congenital defect underlying the calcified aortic cusps.

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A SUCCESSFUL METHOD FOR VACCINATION AGAINST ACUTE ANTERIOR POLIOMYELITIS.*

PRELIMINARY REPORT.

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WITH THE ASSISTANCE OF MISS ANNA M. RULE.

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WE have recently shown[1] that it is possible to successfully vaccinate Macacus rhesus monkeys against acute anterior poliomyelitis by subcutaneous and intracutaneous injections of a vaccine of monkey poliomyelitic cords treated with sodium ricinoleate (Wm. S. Merrell Company). McKinley and Larson[2] had previously found

* Aided by a grant from the Daniel J. McCarthy Fund for Research in Neurology, Temple University.

that monkeys could be sometimes immunized by intraperitoneal injections of this type of vaccine.*

During the past year we have successfully vaccinated 17 additional monkeys with vaccines prepared as follows:

1. Healthy adult Macacus rhesus monkeys, weighing 4 or more kg. of weight, were inoculated intracerebrally (frontal lobe) with 0.2 cc. of a 5% emulsion of monkey poliomyelitic cord (Rockefeller Institute strain) under ether anesthesia.

2. Symptoms of poliomyelitis usually developed in 5 to 9 days and immediately after death, or when the infection was very severe, the hair was sprayed with 5% tricresol solution and the skin over the head and back removed. The cords were then removed under aseptic precautions after the method of removing spinal cords from rabbits in the preparation of rabies vaccine by the original Pasteur method and 8 gm. of a mixture of several cords thoroughly emulsified aseptically in 100 cc. of sterile physiologic saline solution.

3. After fine-mesh filtration under aseptic conditions there was added an equal volume of a sterile 2% solution of sodium ricinoleate in saline solution.†

4. This gave a 4% suspension of mixed tissue in 1% sodium ricinoleate.

5. The mixtures were well mixed and placed in an incubator at 37° C. for 24 hours and then in a refrigerator at 4° to 6° F. for 14 days with daily shaking for a few minutes.

6. Subcultures were made and the vaccines kept in the refrigerator throughout the year. Even though sodium ricinoleate is of low bactericidal activity,[3] we have found that the final concentration of 1% is usually sufficient for sterilizing the vaccines when slight contamination had occurred in the removal of some of the cords and the preparation of the emulsions.

Our previous vaccine[1] was a final 1% emulsion of poliomyelitic cord in a 10% solution of sodium ricinoleate, so that the present vaccines were 4 times as strong in virus (4%) with a lower concentration of sodium ricinoleate (1%). Furthermore, the present vaccines were a mixture of several cords in order to better equalize the amount of virus present, as this sometimes varies in individual cords.

Results. 1. Six monkeys were given subcutaneous injections of 0.05 to 1 cc. per kg. every 5 days for 10 injections and 2 additional animals were given 0.1 cc. by intracutaneous injection every 5 days for 10 injections. None developed the slightest clinical evidences of poliomyelitis during the period of immunization and all remained perfectly well. When inoculated intracerebrally with 0.2 cc. of 5% suspension of fresh virus (about 18 minimal infective doses) 1 month after the last dose, none developed the slightest clinical evidences of poliomyelitis, whereas controls inoculated at the same time developed poliomyelitis in 5 to 9 days and succumbed.

2. Seven monkeys were given subcutaneous injections of 0.1 to 1 cc. per kg. every 5 days for 5 injections and 3 additional animals

* We are indebted to Wm. S. Merrell Company for permission to use sodium ricinoleate in the preparation of vaccines (Patent No. 1621118).

† Sterilized by boiling for 10 minutes.

0.1 cc. per kg. by intracutaneous injection every 5 days for 5 doses. None of these animals developed the slightest clinical evidences of poliomyelitis during the period of immunization. When inoculated intracerebrally with 0.2 cc. of 5% suspension of fresh virus 1 month after the last dose, all remained perfectly well except 1 receiving 5 doses of 0.1 cc. per kg. by subcutaneous injection, which developed poliomyelitis 6 days after inoculation progressing to paralysis but surviving. All unvaccinated controls developed poliomyelitis in 5 to 7 days after inoculation.

3. When the vaccinated monkeys were reinoculated intracerebrally 7 months later with 0.2 cc. of 5% suspension of virus, all remained healthy and well and presented no clinical evidences of poliomyelitis. When reinoculated again 3 months later, or about 10 months after vaccination, all but 1 again remained perfectly well and free of all clinical evidences of poliomyelitis so that at this time it may be stated that the immunity has persisted in all but 1 monkey for at least 10 months after vaccination.

These results have shown, therefore, that it is possible to vaccinate Macacus rhesus monkeys with 5 injections of sodium ricinoleated vaccine in dose of 0.1 cc. per kg. given every 5 days. The subcutaneous injections of 0.05 cc. per kg. also produced effective immunity. Smaller doses may be likewise effective but so far have not been used. Intracutaneous injections may produce more effective immunity than subcutaneous injections but are too painful, as we know from personal experience (J. A. K.); furthermore, it is likely to be impossible to immunize human beings by this route of immunization unless a larger number of injections are given.

Sodium ricinoleate, however, in the amounts employed, does not completely kill the virus. As previously stated, none of the vaccinated animals showed the slightest evidences of poliomyelitis during or following the period of immunization, but the intracerebral inoculation of monkeys with 0.3 cc. of a vaccine 5 months after its preparation produced mild paralysis about 12 days later and showing thereby the survival of devitalized virus in the vaccine.

All attempts to vaccinate with "dead" vaccines sterilized with heat and various chemical agents by others and ourselves[1] have met with no success. It appears that the vaccine to be effective must contain some living but devitalized virus. Subcutaneous and intracutaneous inoculation of monkeys with a vaccine of fresh virus sometimes produces poliomyelitis and, therefore, cannot be utilized for the vaccination of human beings. Sodium ricinoleate, however, in the amounts employed, appeared to sufficiently devitalize the virus to make subcutaneous and intracutaneous injections entirely safe for the monkeys and yet leaving sufficient virus for engendering effective immunity.

We have taken 0.5, 1.5 and 2 cc. of the vaccine by subcutaneous injection every 5 days. The injections were accompanied by some

stinging pain, especially after the first but less after the second and third injections, which quickly subsided, but there was little or no local reaction except in the 2-cc. doses when the local reactions were comparable to those produced by the subcutaneous injection of rabies vaccine. Fever and constitutional reactions, however, were not produced in us, and, while we have found large doses of sodium ricinoleate by intramuscular injection capable of producing some tissue necrosis in rabbits,[3] yet such were not produced in ourselves by even 2-cc. amounts of this poliomyelitis vaccine.

Fortunately for these experiments our blood sera before inoculation were free of antiviral properties, as determined by mixing 0.2 cc. of serum with 0.2 cc. of 5% suspension of virus and injecting the mixture, after standing 2 hours, intracerebrally into 2 monkeys. Both animals developed poliomyelitis in about 7 days.

That the 3 doses of vaccine produced antiviral antibody was shown, however, by repeating the test 2 weeks after the last dose of vaccine, when 2 additional monkeys inoculated intracerebrally with a mixture of 0.2 cc. of serum and 0.2 cc. of 5% suspension of virus allowed to stand for 2 hours, remained perfectly well, whereas a control inoculated with virus alone developed paralysis in 6 days and finally succumbed. These results have shown, therefore, that in the case of ourselves the vaccine was apparently capable of producing antibody for the poliomyelitis virus and probably sufficient for engendering immunity.

It appears to us that this is the only effective method for determining whether or not a vaccine is capable of engendering immunity against poliomyelitis in human beings, because an injection of virus as a test for immunity as done with monkeys is, of course, not permissible, and to vaccinate a group of children to determine over a period of years how many, if any, develop poliomyelitis as controlled by the incidence among a group of unvaccinated individuals would require the immunization of a very large number in the presence of an epidemic. The serum-antiviral test before and after vaccination, however, may be a quicker and more decisive test for acquired immunity, and especially when conducted with children, who are not as likely to have natural antiviral antibody in their sera.

Discussion. We naturally hesitate to advise the subcutaneous injection of a vaccine known to contain some living virus, even though we believe it to be sufficiently devitalized with sodium ricinoleate to make it a safe procedure as determined by the results observed among vaccinated monkeys and ourselves, but we believe that 3 subcutaneous injections of this kind of vaccine at intervals of 5 to 7 days and in dose of from 0.05 to 0.1 cc. per kg. of weight is a safe and effective method for vaccination against acute anterior poliomyelitis.

Indeed, if it is true that human beings acquire immunity to acute anterior poliomyelitis by contact with the virus even without

demonstrable evidences of infection, it would appear that less vaccine may be required per body weight than in the case of monkeys, and especially since less antibody is probably required for the protection of human beings against small amounts of virus entering the upper respiratory tract than required for the protection of monkeys inoculated intracerebrally with 15 to 20 minimal infective doses.

Since these vaccines never produced the slightest evidence of infection in the monkeys and ourselves, and believing that the amount of sodium ricinoleate employed effectively reduces the virulence of the virus, we are at present vaccinating a group of children varying in age from 8 months to 15 years. These have been selected after preliminary antiviral tests with monkeys have shown the absence of antibody in the sera. Three doses are being given at weekly intervals with monkey antiviral tests with the sera of some children after the first and second doses and with the sera of all children after the third dose in order to determine the rapidity of antibody production and the number and size of doses of vaccine required.

The first dose for children under 3 years has been 0.25 cc. and 0.5 cc. for older children up to 15. By making the first dose quite small in this manner and waiting 7 days, opportunity is afforded for antibody production before the second and third doses are administered. Varying amounts are being given in the second and third doses and a subsequent report will soon be made on the results, along with further details on the preparation and standardization of the vaccine. Since the cord of a large-sized monkey will yield about 200 cc. of vaccine, and taking a total of 3 to 4 cc. for the immunization of a child, 1 monkey will yield sufficient vaccine for the immunization of 50 or more children. If subsequent experiments now under way show that it is possible to prepare vaccine of monkey poliomyelitic brain, the yield would be much larger and the cost correspondingly less.

While one may question the importance of vaccination against poliomyelitis in view of the low incidence of the disease, yet I became convinced of its advisability 2 years ago when thoroughly reviewing the situation before commencing these investigations and will present the reasons at the same time.

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POLIOMYELITIS.

A Study of 410 Patients at the Philadelphia Hospital for Contagious Diseases.

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During the summer of 1932, Philadelphia experienced its second epidemic of poliomyelitis. The greatest portion of the reported cases was sent to this hospital for diagnosis and treatment. Four hundred and ten persons suspected of having fallen victims to this dreaded disease were sent to us between the months of July and November. It is not necessary to mention that all were not cases of poliomyelitis. As is common during an epidemic, some patients are wrongly but justifiably suspected.

From the outset we were confronted with the problem of abortive poliomyelitis. What cases should be and what cases should not be diagnosed as such? Were we justified in venturing such a diagnosis from a hospital viewpoint? After careful consideration it was deemed advisable not to make this diagnosis, as the margin of accuracy was too narrow. Accordingly no patient was discharged from this hospital as one of abortive poliomyelitis, although, to be sure, many cases might have been designated as such. The diagnosis of poliomyelitis was only made when the patient presented the accepted clinical and pathologic picture. Positive spinal fluid findings were obtained in most cases. The patient was discharged with a diagnosis of poliomyelitis with or without paralysis. It was found difficult in some cases, especially infants, accurately to determine the presence or degree of weakness or paralysis.

Routine. On admission, patients were examined, spinal puncture was performed, the fluid immediately studied and treatment instituted. Doubtful cases were isolated until a definite diagnosis could be made. Immune serum was given to all patients in whom it was felt that an active progressive infection was present, irrespective of the presence or absence of paralysis. Patients with definite evidence of paralysis, but without evidence of progress or extension of paralysis, were not given immune serum. The immune sera consisted of convalescent and contact serum. Whole blood was also used. The last 2 were given intramuscularly, the former intravenously. It was attempted to give a total of 100 cc. of immune serum divided into 40 cc. of convalescent and 60 cc. of contact. We did not have a control group.

Two respirators were in constant use throughout the epidemic. At times, because of this limited number of respirators, it was

necessary to transfer patients to other hospitals for treatment. In this way, 8 of our patients were treated by neighboring hospitals. These are not included in this study.

Quarantine. It was not thought necessary to keep patients in this hospital for 21 days. Of course, some were kept the full time, either because of the severity of the illness, or because of the lack of proper home facilities. The majority of patients were detained between 10 and 15 days. The average number of hospital days for the entire group was 10.6. When the temperature, pulse and respirations were normal for about 7 days, and there was no evidence of extension of paralysis, patients were transferred to their homes in our ambulances. The balance of the quarantine period was then maintained at home. As far as we can determine, no secondary cases were experienced because of this practice.

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF 410 CASES REFERRED AS POLIOMYELITIS.

	No. of cases.	Percentage of total.
Poliomyelitis	304	74.1
La grippe	31	7.6
Gastro-intestinal upset	16	3.9
Tonsillitis	13	3.2
Bronchopneumonia	6	1.5
Lobar pneumonia	6	1.5
No disease	3	0.7
Bronchitis	2	0.5
Localized meningitis	2	0.5
Acute pharyngitis	1	0.2
Tracheobronchitis	1	0.2
Rheumatic fever and rheumatic endocarditis	1	0.2
Scarlet fever	1	0.2
Rheumatoid arthritis	1	0.2
Catarrhal jaundice	1	0.2
Hysteria	1	0.2
Pulmonary tuberculosis and tuberculous meningitis	1	0.2
Typhoid fever	1	0.2
Arthritis of hip	1	0.2
Influenzal meningitis	1	0.2
Cerebrospinal meningitis	1	0.2
Acute peritonitis and ruptured diverticulitis	1	0.2
Food allergy	1	0.2
Anterior spinal thrombosis	1	0.2
Acute arthritis	1	0.2
Chorea	1	0.2
Poison ivy	1	0.2
Drug rash	1	0.2
Alcoholism	1	0.2
Pyelitis	1	0.2
Acute otitis media	1	0.2
Scurvy and rickets	1	0.2
Acute sinusitis	1	0.2
Vincent's angina	1	0.2
Tuberculous meningitis	1	0.2

In all, 410 patients were admitted as suspected cases of poliomyelitis. This diagnosis was confirmed in 304 (74.1%). In 106 (25.9%) this diagnosis was disproved. No doubt, as can be seen in Table 1, the diagnosis in some of these cases might be disputed.

Some could have easily fitted into the picture of the so-called abortive type of poliomyelitis; but in the majority of cases the diagnosis was clear-cut. The difficulty attending a diagnosis of abortive poliomyelitis is admitted by all physicians. Indeed, in a study of 446 cases of suspected poliomyelitis referred to the Herman-Kiefer Hospital in Detroit, Gordon[1] could only verify this diagnosis in 50.2% of this number.

Age, Sex, Race. In all, 304 cases of poliomyelitis were treated, ranging in age from 4 months to 52 years. Twelve (5.6%) were under 1 year. The youngest patient was a female child, aged 4 months. The ratio of male to female was equal in this age group. The largest number of patients fell in the age group of 0 to 4 years, inclusive. This formed 47.7%. In other words, 53.3% of those affected were children under 5. These figures correspond to the unpublished age-group figures of the New York City epidemic of 1931.[2] The next highest number of cases occurred in the 5 to 9 years group, representing 27.6%. The small number of 1.3% represents the 20 years or more age group. As to the ratio of male to female, the male group predominated 188 to 116.

TABLE 2.—PERCENTAGE DISTRIBUTION BY AGE GROUPS.

	Cases, 304. Per cent.
Under 1 yr.	5.6
0 to 4 yrs.	47.7
5 to 9 "	27.6
10 to 14 "	13.2
15 to 19 "	4.6
20+ "	1.3

TABLE 3.—AGE AND SEX INCIDENCE.

	Male.	Female.	Ratio: Males to 1 female.
Under 6 mos.	..	2	
6 mos. to 1 yr.	9	6	1.50
12 mos. to 1½ yrs.	14	7	2.00
18 mos. to 2 "	34	18	1.89
3 yrs.	18	14	1.29
4 "	22	18	1.22
5 "	12	7	1.71
6 "	15	10	1.50
7 "	11	8	1.38
8 "	8	5	1.60
9 "	6	2	3.00
10 "	6	4	1.50
11 "	4	2	1.50
12 "	7	4	1.75
13 "	6	3	2.00
14 "	3	1	3.00
15 "	1		
16 "	2	1	2.00
17 "	1	1	1.00
18 "	3	1	3.00
19 "	2	2	1.00
20 to 24 yrs.	3		

It was noted that as the epidemic progressed into the months of September and October, patients ranging in the group of 5 to 9 years predominated, while in the early months of the outbreak the age group of 0 to 4 years was prevalent.

The race study shows a remarkable increase among negroes in comparison with the 1916 epidemic. This is undoubtedly due to the tremendous increase in the negro population in Philadelphia since the 1910 census. In 1910, the total population of this city was given as 1,724,630. Of this number, there were 84,459 blacks (4.89%). In the census of 1930, with a total city population of 1,978,879, there were 219,599 blacks (11.09%). The actual increase in the colored population in Philadelphia from 1910 to 1930 is 135,140 (160%). However, if we consider the percentage of whites to blacks, we will find that the percentage increase of blacks is 6.2%. The number of poliomyelitis patients among the blacks admitted to this hospital in 1916 is 2.9%; whereas in 1932 it was 15.5%. This shows an increase of 12.6% of blacks contracting poliomyelitis, in comparison to an increase of 6.2% population. Undoubtedly, there was a greater percentage of susceptibles among the blacks, for it is interesting to note that of the total increase of 254,249 in the total population of Philadelphia from 1910 to 1930, 135,140 (53.5%) were black.

Symptomatology. The information recorded with reference to the onset of the present illness and the history of past diseases was obtained by the ambulance nurse from parents in most cases. It is needless to say that in some instances this information was given inaccurately. The correctness of the data obtained in this respect is in direct proportion to the intelligence of the parents and the ability of the questioner to elicit the information. In most cases, parents were found to be good observers, but in a small number their observations were inaccurate. However, we feel that a fairly good picture can be drawn from the information on hand.

The usual order of symptoms—fever, vomiting and headache—prevailed in the majority of patients admitted. As will be seen in Table 4, fever marked the onset of poliomyelitis in the majority of cases, nausea, or vomiting and headache ranging second and third, respectively. Among the less common symptoms of onset, drowsiness was the leader.

The most prevalent physical sign observed was the absence of knee jerks. Superficial and deep reflexes were next in order. Rigidity or stiffness of the neck was present among a goodly portion. These percentages may seem slightly high, but it must be remembered that about 50% of the patients showed on admission some signs of weakness or paralysis.

As mentioned above, 304 patients were discharged with a diagnosis of poliomyelitis. Of this number, 192 (63.2%) showed some evidence of weakness or paralysis. The distribution of paralysis

in this group was mostly centered in one extremity, either the arm or leg, with paralysis of both extremities next most common.

TABLE 4.—INCIDENCE OF SIGNS AND SYMPTOMS.

		Per cent.
Fever		81.58
Nausea and vomiting		52.63
Headache		48.68
Drowsiness		21.05
Hyperesthesia		7.89
Irritability		6.91
Excessive sweating		5.59
Sore throat		5.59
Apprehensiveness		3.94
Restlessness		3.94
Constipation		2.63
Diarrhea		2.24
Coryza		1.64
Knee jerks	Absent	53.32
Superficial reflexes	Absent	49.68
Deep reflexes	Absent	47.04
Stiffness of neck	Present	40.13
Kernig	Present	22.37
Babinski	Present	10.86
Muscular twitching	Present	5.26
Spine sign	Present	3.62
Muscular tremor	Present	2.96

TABLE 5.—DISTRIBUTION OF PARALYSIS.

Both legs	29
One leg	64
Both legs and both arms	11
Both legs and one arm	8
One arm	33
One arm and one leg (same side)	4
One arm and one leg (opposite side)	0
Both arms	12
Both arms and one leg	3
Trunk	9
Facial alone	16
Throat or neck	3
Total	192

Etiology. It was attempted to determine what part the occurrence of other acute infections played toward the production of immunity against poliomyelitis; whether the absence or presence of tonsils makes one more susceptible; and if vaccination against smallpox or diphtheria prophylaxis increases the resistance of a child to poliomyelitis. A résumé of the history in each case shows that 64.1% of the poliomyelitis patients suffered from one or more attacks of the acute infections of childhood. Tonsils were present in 81.6% of the group of cases. It was not noted whether the tonsils presented evidence of disease. Amoss and Taylor[3] have shown that the healthy nasopharynx furnishes virucidal substances. From their observation we may assume that the nasopharynx was diseased in this group of patients; 56.3% had been vaccinated

against smallpox and 51.3% had toxin-antitoxin prophylaxis against diphtheria.

Laboratory Data. Spinal fluid examinations showed the usual findings. The fluid was clear in color, under increased pressure in most cases. A fibrin web formed, upon standing, in a small number of cases. The average cell count was 93 leukocytes, the lowest 2 and the highest 1067. The predominating type of cell was the lymphocyte.

Treatment. In the absence of any definite specific for the treatment of poliomyelitis, convalescent and contact serum was used. The majority of patients were given serum on admission. A smaller group of patients, who presented definite evidence of paralysis, or in whom there was great doubt as to the presence of poliomyelitis, were not given serum. Of the 304 cases of poliomyelitis, 254 (83.55%) received serum; 50 (16.45%) did not. Among those who received serum (254), 124 presented evidence of weakness or paralysis on admission; 130 did not. Eighty-five of those showing evidence of weakness or paralysis (124), and 96 of those showing no evidence of weakness or paralysis (130) were admitted during the first 4 days of the disease. On discharge it was found that 154 (60.63%) of those receiving serum showed evidence of weakness or paralysis, an increase of 30 patients. Of the 50 who did not receive serum, 28 showed evidence of weakness or paralysis and 22 did not. Ten of the former and 14 of the latter were admitted during the first 4 days of the disease. On discharge, 38 showed evidence of weakness or paralysis and 12 did not.

TABLE 6.—DATA ON SERUM TREATMENT, PARALYSIS, MORTALITY.

Day of disease.	No. of cases in group.	Serum.				No serum.				Died.	
		Weakness or paralysis.		No weakness or paralysis.		Weakness or paralysis.		No weakness or paralysis.			
		On admission.	On discharge.	On admission.	On discharge.	On admission.	On discharge.	On admission.	On discharge.	Serum.	No serum.
1 . .	61	16	22	37	31	2	3	6	5	4	0
2 . .	45	20	25	20	15	2	4	3	1	2	1
3 . .	54	24	32	23	15	3	5	4	2	4	2
4 . .	45	25	27	16	14	3	4	1	0	3	0
5 . .	34	10	13	15	12	6	7	3	2	1	0
6 . .	23	9	12	8	5	5	6	1	0	0	2
7 . .	16	8	11	5	2	2	3	1	0	0	1
8 . .	10	4	3	1	2	3	3	2	2	2	0
9 . .	1	0	0	1	1	0	0	0	0	1	0
10 . .	3	2	2	0	0	0	1	1	0	0	0
11 . .	2	0	0	0	0	2	2	0	0	0	0
12 . .	2	2	2	0	0	0	0	0	0	0	0
13 . .	1	1	1	0	0	0	0	0	0	1	0
14 . .	2	0	0	2	2	0	0	0	0	0	0
15 . .	2	2	2	0	0	0	0	0	0	0	0
? . .	3	1	2	2	2	0	0	0	0	0	0
	304	124	154	130	100	28	38	22	12	18	6

In all, there were 192 (63.2%) cases with evidence of weakness or paralysis, while 112 (36.8%) showed no evidence of paralysis.

There occurred 24 deaths, a percentage death rate of 7.89. Of the 24 patients who died, 18 received serum and 6 did not; 22 (91.67%) patients died within the first week of their disease. Two (8.33%) died within the second week.

TABLE 7.—DEATHS FROM POLIOMYELITIS BY DAY OF DISEASE.

	Deaths.	Per cent.
First day	3	
Second day	4	
Third day	6	
Fourth day	3	
Fifth day	1	
Sixth day	2	
Seventh day	3	
First week	22	91.67
Second week	2	8.33
Total	24	

TABLE 8.—SUMMARY OF DATA ON SERUM THERAPY AND RESULTS.

	Serum.	No serum.
Admitted with paralysis	124	28
Died	11	6
Admitted without paralysis	130	22
Died	7	0

Of the 24 patients who died, 17 required the use of the respirator; 10 of the 17 succumbed despite the use of respirator; 7 recovered from respiratory paralyses but subsequently died. The respirator was a great aid in relieving those with evidence of transitory paralysis. Patients who required the respiratory longer than 72 hours did not fare well. Several patients recovered after several days in the respirator. However, investigation shows that these patients died later of some other disease. A careful check-up is being made on these patients at present.

TABLE 9.—SUMMARY OF DATA.

Total No. of cases.	Total paralysis.		Serum treated.			No serum.			Deaths.			Mort., per cent.
			Paralysis.		Total.	Paralysis.		Total.	Serum.		Total.	
	Yes.	No.	Yes.	No.		Yes.	No.		Yes.	No.		
304	192	112	154	100	254	38	12	50	18	6	24	7.89

Summary. 1. During the summer and fall of 1932, 410 patients were admitted to this hospital as suspected cases of acute anterior poliomyelitis. The diagnosis was verified in 304 (74.1%).

2. The majority of those affected were in the age groups of 0 to 4 years and 5 to 9 years, 53.3% in the former and 27.6% in the latter. There were 188 males and 116 females. As to race, 84.5% were whites and 15.15% were negroes.

3. Two hundred and fifty-four patients (83.5%) received serum; 124 of these showed evidence of weakness or paralysis on admission. Upon discharge from the hospital this number increased to 154.

4. Fifty patients (16.5%) received no serum on admission. Of this number, 28 showed evidence of weakness or paralysis. Upon discharge this number increased to 38.

5. One hundred and ninety-two (63.2%) of the patients were discharged with evidence of paralysis; whereas on admission 152 (50%) presented such evidence.

6. There occurred 24 deaths (7.89%). Eighteen of this number received serum; 22 of the deaths occurred within the first week of the disease, 2 in the second week.

7. Of the 24 fatal cases, 17 required the use of the respirator; 10 of this number died while in the respirator.

Conclusion. In view of the above findings, the conclusion seems justified that convalescent serum was of little value in the prevention of paralysis.

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ENCEPHALITIS IN CHILDREN APPARENTLY CONGENITAL AND FOLLOWING MATERNAL INFLUENZA.

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Influenza is recognized as being one of the most serious infections which may complicate pregnancy. Miscarriages, abortions, and premature labor are frequently induced by an attack of this disease and the mortality rate is definitely higher in pregnant than in non-pregnant women. Jordan[1] concludes, after an extensive review of the literature, that an attack of influenza is more serious in the later than in the earlier months of pregnancy; that severe influenza is more likely to cause interruption of pregnancy than a mild attack of the disease, while the mortality rate is higher in those cases in which the pregnancy has been interrupted.

Death of the fetus is a frequent, but not invariable result of maternal influenza. Welz[2] reported a fetal mortality of 66 per cent in his series of 21 cases, and noted that fetal mortality is lessened when the mother recovers. This high fetal mortality rate has been variously ascribed to premature delivery, to toxemia, to hyperpyrexia, to anoxemia, and to direct infection through the placenta.

Very few reports of autopsies on these infants can be found, however, and none includes an examination of the central nervous system. Abt[3] reported a 2 weeks' premature infant born of a woman suffering with influenza, who at birth presented signs of an upper respiratory infection with râles in the chest and cyanosis. It died on the third day. Pathologic examination revealed hemorrhagic bronchopneumonia and septic endocarditis. Streptococci were present in all organs examined. Townsend's[4] case was a 2 weeks' premature infant who had signs of influenza at birth, the mother having developed the disease 1 week prior to labor. Two cases of bronchopneumonia, developing 18 to 24 hours after delivery of mothers suffering with influenza, were reported by Woolston and Conly.[5]

Kosmak,[6] in a series of 21 cases of maternal influenza, reported that 3 children were born alive and died postpartum, 1 was stillborn, and 3 were aborted after the 5th month, while 2 mothers died undelivered. He also observed that many of the surviving infants were definitely below par. Other than this, however, it does not appear that any observations have been made concerning the subsequent health and development of the children.

Fortunately, in the literature on epidemic encephalitis complicating pregnancy, more statistics are available regarding the subsequent history of living children and on autopsy findings of the dead infants. This disease is not so fatal to the pregnant woman or the fetus as is influenza. However, fetal deaths have occurred, and in several the postmortem findings showed changes characteristic of epidemic encephalitis. In Marinesco's case,[7] a classical one of this kind, the mother died of epidemic encephalitis about 3 months before term after an illness of 3 weeks. The death of the fetus took place a day before that of the mother, as evidenced by absence of fetal movements and heart sounds. Pathologic examination of the brains of both mother and child revealed the typical perivascular cuffing characteristic of epidemic encephalitis. A similar case was reported by Kononowa.[8] Santi[9] and Balaban[10] each reported a case of epidemic encephalitis in an infant born of a mother who was suffering with this disease. In each case, autopsy findings confirmed the clinical diagnosis. These 2 cases, however, might have been owing to contact.

Symptoms of epidemic encephalitis have been observed to develop in infants nursed by mothers attacked with encephalitis, by Hallé,[11] and also by Klippel and Baruk.[12] The autopsy of Hallé's infant

revealed no evidence suggestive of epidemic encephalitis, however, while the one reported by Klippel and Baruk recovered.

Roques[13] considers three possible modes of infection from mother to child: (1) by direct contact; (2) through the milk, or, (3) by transplacental passage of the virus, which he favors as being the most probable. This route of infection has some experimental confirmation in that Levaditi, Harvier, and Nicolau[14] demonstrated that the virus obtained from encephalitis in man, can, when inoculated into rabbits, pass through the placenta and localize the fetal nervous system. The cases cited by Marinesco and Kononowa appear to be good evidence in support of this mode of transmission. Thus there seems to be definite evidence that both in the case of influenza and of epidemic encephalitis, transmission from the mother to the child can occur.

The case reports here presented are of interest, not only because the children appear to have congenital encephalitis, but also because they were born of mothers suffering with influenza in the later months of pregnancy. None of these women had symptoms suggestive of epidemic encephalitis. All of them survived the disease and, as far as can be determined, none shows any signs of the sequelæ of encephalitis. The children, on the other hand, show character defects typical of postencephalitic behavior change, and in 5 cases there is evidence of organic involvement of the extrapyramidal system.

Case Abstracts. Case 1.—E. H., white female, born February 1, 1919. The mother had influenza in the 8th month of pregnancy and was delivered of twins at term. One child died at the age of 6 months of "malnutrition." No details concerning her physical condition can be obtained. The case reported is the surviving twin. She had measles and diphtheria, but no other acute illnesses in childhood. The mother states that she has been hyperactive since infancy. She was slow in learning to talk, seemed somewhat mentally retarded, and has always been a serious behavior problem. She was referred to the Graduate Hospital in 1930 for study. Physical examination revealed that she was small and underdeveloped for her age, with mild choreiform tremors. Neurologic examination was otherwise negative. Her I. Q. was 38, but because of her great distractibility this estimate was not considered to be entirely accurate. When seen in April, 1934, her tremors were much more severe and she had a marked dysarthria. Otherwise, her neurologic examination was negative. She is hyperactive, hypersexed, destructive, and vicious. The Wassermann test is negative. Six siblings are apparently normal. The diagnosis of congenital encephalitis was made in this case because the symptoms apparently started at birth and have been progressive. Aside from measles and diphtheria the child has suffered from no acute illness.

Case 2.—R. C., white male, born October 22, 1918. During his mother's severe attack of influenza, the child was born about 2 months premature. The delivery was otherwise uncomplicated. At 3 weeks, the child had severe convulsions, the cause of which was undetermined. As an infant he was delicate and seemed rather stiff. He sat up at 2 years, talked at 4, and walked at 5. He had measles, mumps, and varicella, but no other acute infections. He was referred to the Graduate Hospital in May, 1930. He

was hyperactive, and at the same time tired very easily. He had a marked rigidity of the extrapyramidal type. Tendon reflexes were all hyperactive, but there were no pathologic reflexes. Arm swing was absent on the right and diminished on the left. There was a marked hypersalivation. His I. Q. was 79. The Wassermann test was negative. His mother complained that he was hard to manage and had severe temper tantrums when crossed. The diagnosis of congenital encephalitis was made because of the marked symptoms of a lesion of the extrapyramidal system which has apparently existed since birth.

Case 3.—H. M., a negress, born September 19, 1918. Her mother had influenza at the time of delivery. The child is said to have been born with a "cold" which lasted several weeks. She had measles, mumps, pertussis, and varicella in childhood. Although she developed normally, she was abnormally hyperactive, and has been a serious behavior problem since early childhood. She was referred to the Philadelphia General Hospital for study in 1930 because of her conduct disorder. Physical examination revealed a well-developed but hyperactive child. She had impairment in automatic associated movements, with some rigidity and tremor of the left hand. Tendon reflexes were greater on the left than on the right. Her I. Q. was 80. The Wassermann test was negative. As she grew older, her delinquencies became more serious. Her behavior is of the compulsive type. She is very hyperactive and noisy. She hits and pinches other children. She is immoral. She was finally committed to Byberry in September, 1933, where she causes a great deal of disturbance. Of 5 siblings, 4 are well adjusted. One brother has had some character change following a severe cerebral concussion in 1930. The characteristic behavior change, as well as the signs of organic involvement of the extrapyramidal system, led to the diagnosis of encephalitis in this case. The absence of any symptoms of an acute infection of this nature other than the "cold" she had at birth suggests that the condition is congenital.

Case 4.—E. E., white male, born October 12, 1918. The mother had a slight attack of influenza during the 8th month of pregnancy, from which she entirely recovered. The delivery was normal, but the child did not cry for 24 hours after birth, following which he cried almost incessantly during the first 5 months of life. At 6 months, he had a severe attack of diarrhea, which lasted for several weeks. Aside from this, measles was the only other disease in childhood. He has always been weak on the left side of his body and in addition has been very hyperactive. He was referred to the Graduate Hospital for study in December, 1929. Physical examination revealed marked arrhythmia of winking and rigidity of muscles of the right face, arm, and leg of the extrapyramidal type. Reflexes were greater on the right than on the left, but no pathologic reflexes could be demonstrated. He also had a mild dysarthria and loss of automatic associated movements of the right side. He showed a marked character disorder. He could not be controlled in school, hit other children, and had violent temper tantrums. When last seen in March, 1934, his father asked that he be committed to Byberry, as he feared that he might do harm to the other children in the family. He is of normal intelligence. Four siblings are normal and well behaved. This case is clearly one of encephalitis and is apparently congenital.

Case 5.—A. L., white male, born October 1, 1918. The mother had just recovered from a severe attack of influenza when she fell into labor 1 month before term. The delivery was normal. The child seemed fairly normal at birth, but had several convulsions a few days after. He was slow in developing. He walked at 3 years and talked at 5. He had measles, varicella, and bronchitis in childhood. He was examined at the Philadelphia General Hospital in 1930, and again in 1934. Physical examination showed

some loss of automatic associated movements, asymmetry of finger spacing, slight rigidity of the cog-wheel type, and a marked dysarthria. He was otherwise neurologically negative. He is definitely feeble-minded, having an I. Q. of 30. The Wassermann test was negative. A diagnosis of encephalitis was made in this case on the basis of the neurologic findings. It is apparently congenital.

Case 6.—T. K., white male, born July 20, 1923. The mother had a severe attack of influenza at the time of the child's birth. The delivery was normal but she states that her physician told her that the child was born with a "sleeping brain." The child was very lethargic during the first few months of life, and was very slow in learning to walk and talk. He had measles, varicella, pertussis, and pneumonia in childhood. He was referred to the Graduate Hospital for study in 1928, at which time, he was hyperactive, was unclean in his personal habits and had violent temper tantrums when crossed. Neurologic examination was negative with the exception that his pupils reacted to light but not to accommodation. His I. Q. was 90, and the Wassermann test negative. He is now in an orphanage, where he seems to be making a fairly good adjustment. The history of somnolence, dating from birth, the reverse Argyll-Robertson pupil, a common finding in epidemic encephalitis, and the behavior disorder, led to the diagnosis of congenital encephalitis.

Case 7.—C. H., white male, born April 21, 1919. The mother had influenza in the 7th month of pregnancy, from which she fully recovered and had a normal delivery at term. The child was slow in developing. He walked at 19 months, and talked at 3 years, at which time he had a distinct impediment in speech. He had measles, varicella, and bronchitis in childhood. Since infancy, he has been hyperactive and difficult to control. He was brought to the Philadelphia General Hospital in December, 1927, by his mother, who said she could not manage him. He had taken $8 from her pocketbook, treated the boys in the neighborhood to candy, bought 12 toy balloons and stayed out all night. The delivery man found him in a bread box in front of a grocery store the following morning. Physical examination revealed a very hyperactive boy of 9 years, showing no physical abnormalities. Since then, he has had a long court record. He has stolen many bicycles, which he rides for a while, and then abandons. He is a runaway, and has made physical attacks on several people. He was committed to Glen Mills in 1931 for breaking into a store. He escaped 2 weeks afterward, and has not been heard from since. There are 4 siblings, all apparently normal.

All of these cases have several important features in common. They were born of mothers who had influenza during the later months of pregnancy. Their symptoms have apparently existed from the time of birth. They give no history of acute illness, which might have been epidemic encephalitis, nor in any case did the onset of symptoms coincide with the occurrence of one of the usual diseases of childhood.

In spite of the fact that no corroborative autopsy evidence can be offered, there is little doubt as to the diagnosis in these cases. In 5 there is sufficient evidence of organic involvement of the extrapyramidal system to verify the diagnosis of encephalitic sequelæ. Four are Parkinsonian in type, while the 5th has choreiform tremors, which are increasing in severity. The 6th case gives a definite

history of lethargy which was first noticed at birth. In addition, examination of his pupils revealed the reverse Argyll-Robertson phenomenon, which is recognized as being a common sequel of epidemic encephalitis. The 7th was the only case in which the physical findings were negative. Here, the diagnosis was based on the type of behavior disorder.

Postencephalitic behavior, like the behavior seen frequently following cerebral concussions and in a milder form complicating Sydenham's chorea, is definitely compulsive in type. It seems to be owing to lack of inhibition rather than to willful antisocial tendencies. These individuals are seized by uncontrollable impulses which they are compelled to follow and afterward are at a loss to explain. All of the children, except A. L., who is an imbecile, show this characteristic type of behavior, while C. E., unhampered by physical infirmities, is the best illustration of it.

The majority of these cases, therefore, present both the behavior disorder as well as the organic signs characteristic of the sequelæ of epidemic encephalitis. They appear to be congenital and follow maternal influenza.

The possibility of a relationship between influenza and epidemic encephalitis has been implied by some clinical evidence. The coincidence of the two recent epidemics, the definite encephalitic symptoms, such as somnolence and diplopia, which sometimes accompany an attack of influenza, and the occurrence of clear-cut cases of encephalitis during epidemics of influenza, suggest the kinship of these two diseases. It is also a well recognized fact that many individuals presenting unmistakable signs of chronic encephalitis give a definite history of having had influenza, but, on the other hand, have never had symptoms suggestive of acute encephalitis. However, it must be added that it is not always possible to obtain a history of either infection in these cases. In addition, there is some bacteriologic evidence that the influenza bacillus may be the etiologic factor in epidemic encephalitis. The work of Crofton,[15] as well as that of the writer in collaboration with Evans,[16] strongly suggests this hypothesis. Since the 1918 epidemic, however, the Pfeiffer bacillus has fallen into abeyance as the sole causal factor in influenza.

While the cases cited in this report cannot be accepted as proof of the existence of a common etiologic factor in these two diseases, they suggest that such may be the case. While keeping in mind the possibility of the *post hoc ergo propter hoc* fallacy in these cases, it is worth while to investigate the prenatal histories of children showing signs of chronic encephalitis, not preceded by an acute attack of the disease. In all cases of fetal death, as a result of maternal influenza, the autopsy should include an examination of the central nervous system.

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INSULIN ALLERGY. TREATMENT WITH HISTAMIN.

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Since the introduction of insulin into the therapy of diabetes, it has been observed that a certain percentage of these insulin-treated cases develop either reactions at the site of injection, or general reactions which are quite characteristic of protein sensitization. The literature of the past 10 years contains a number of reports of insulin-treated patients who developed these allergic reactions. A complete review of this subject up to 1932 is found in an article on insulin allergy by Allan and Scherer.[1] An excellent study of the immunologic considerations of insulin hypersensitiveness was made by Tuft.[2]

When a diabetic patient on insulin treatment develops a protein reaction, the problem becomes a very disconcerting one, particularly if the diabetes is so severe that its management and control require the continued use of insulin. The incidence of patients experiencing sensitization reactions, among insulin-treated cases, is a significant one. Allan and Scherer report it as high as 14.1% in a collected series of over 1800 diabetics. Lawrence,[3] in 1925, observed these

reactions in as many as 30% of his cases. We have collected 407 cases of insulin-treated diabetics in the past 3 years and have found 30 patients who developed protein reactions, an incidence of 7.3%.

Although there have been sporadic case reports of generalized urticarial reactions,[2] all of our cases gave only local reactions. Of the 30 cases in our series, 27 showed local reactions beginning between the 7th and 15th day after insulin therapy was instituted. Three cases developed reactions after 3 weeks of treatment. The reactions were uniformly characteristic in all cases, and differed only in degrees of severity. They were characterized by the development, between 1 and 6 hours after the injection, of a localized swelling, redness, heat, surrounding erythema, severe itching and pain at the site of injection. These reactions would last, in some cases, as long as 36 hours and then subside spontaneously. The symptoms would frequently become so distressing that some means had to be found to relieve the patients. Just as with other observers, our experience has been that merely changing the commercial type of insulin used was sufficient to make a continuation of the treatment possible. Twenty-five patients responded to this form of treatment. Five patients showed reactions to all types of insulin, so that it became imperative that diabetic treatment be continued with dietetic restrictions alone (Table 1).

Attempts at desensitization have frequently been employed and sometimes successfully. We have used this procedure with 2 patients who showed positive skin tests to all types of insulin, including crystalline insulin. Desensitization, with commercial Lilly insulin, was started in both cases with 0.0001 unit and gradually increased by doubling the dose every other day. When 0.1 unit was reached, the dose was increased by tenths of a unit. The procedure was necessarily long and covered a period of 3 months. At the end of this period, both patients were able to tolerate as much as 15 units in a dose, given twice a day. Desensitization, however, lasted only for 1 month. Both patients again began to show local reactions so that it became necessary to stop the insulin. One year later 1 of these patients experienced an infection of a foot with a severe break in sugar tolerance. Insulin therapy was indicated and employed with the development of such mild local reactions that it was possible to continue using it.

Spontaneous desensitization has been reported in a few cases of insulin allergy. Sturtevant,[4] in 1924, reported a case of a diabetic patient who developed a local, hard, painful nodule at the site of injection. The skin over the nodule was hot to the touch, red, raised and clearly marked off from the normal skin. The reaction lasted 72 hours and then gradually disappeared. These lesions appeared after every injection for 6 weeks, then became less severe and soon disappeared completely, so that the patient was able to take insulin without any discomfort. Lasersohn,[5] in 1930, reported

a case of a patient who developed a local reaction at the site of injection. After 3 weeks, the local reaction was less marked, and in another week had entirely disappeared.

TABLE 1.—RESULTS OF TREATMENT IN 30 DIABETICS WITH LOCAL INSULIN REACTIONS.

Name.	Type of reaction.	Onset of reaction, No. of days after beginning insulin.	Type of insulin to which patient was sensitive.	Treatment.	Results.
J. A.	Local	14	Lilly	Histamin	Good.
L. A.	Local	24	Lilly	Special	Relieved; able to take regular insulin in 9 mos.
S. A.	Local	10	Stearns	Special	Relieved.
D. B.	Local	10	Lilly	Special	Relieved.
S. C.	Local	15	Lilly	All brands insulin	Sensitive; insulin discontinued.
L. D.	Local	15	Stearns	Special	Relieved
B. D.	Local	8	Squibb	Special	Relieved.
M. D.	Local	11	Lilly	All brands insulin	Sensitive; insulin discontinued.
S. E.	Local	10	Lilly	Special	Relieved.
R. E.	Local	9	Lilly, Lilly Spec. and Mulford	Squibb	Relieved.
F.	Local	10	Squibb	Special	Relieved.
R. F.	Local	11	Lilly	Lilly Spec., Hog, Mulford	Relief in 2 mos.
S. F.	Local	..	Stearns	Special	Relieved.
H. G.	Local	10	Lilly	Special	Relieved; no reaction to regular insulin 6 wks. later.
F. G.	Local	12	Lilly	Special	Relieved.
P. G.	Local	10	Lilly	Mulford, Stearns Spec.	Sensitive; insulin discontinued.
J. H.	Local	10	Squibb	Special	Relieved.
H. H.	Local	9	Lilly	Lilly Spec., Hog insulin	Relieved; later able to take regular insulin.
R. L.	Local	7	Lilly	Lilly Spec., Hog	Sensitive; insulin discontinued.
P.	Local	6	Stearns	Hog, Spec.	Able to take special insulin after 1 mo.
L. R.	Local	10	Lilly	Mulford, Lilly Spec.	Relieved by Mulford.
E. S.	Local	9	Lilly	Special	Relieved.
S. S.	Local	9	Lilly	Special	Relieved.
M. S.	Local	7	Lilly	Special	Relieved; 6 wks later took regular insulin.
H. S.	Local	10	Lilly	Special	Relieved; 2 mos. later took regular insulin.
M. S.	Local	30	Lilly	Special	Relieved.
R. T.	Local	10	Lilly	Special	Relieved; 1 mo. later no reaction to regular insulin.
S. F.	Local	10	Stearns	Special	Relieved.
H. S.	Local	12	Lilly	Special	Relieved.
E. R.	Local	11	Lilly	Special	Relieved.

Some reports have recently appeared of cases of urticaria due to physical causes, which have demonstrated a remarkable therapeutic response to the use of histamin injections. Bray[6] reported the case of a boy, aged 8, who experienced localized and generalized allergic reactions to cold water. Placing his hand in cold water at a temperature of 45° F. resulted in localized redness, swelling and itching of the immersed hand, followed by generalized symptoms of headache, faintness, dyspnea, cough and a depression in temperature and blood pressure. A successful immunity to this form of physical allergy was affected by repeated injections of histamin hydrochlorid. Mueller[7] reported the case of a woman, aged 29, who developed periodic edema of the left hand, occurring every 14 days and lasting for 7 days, which had been treated with milk and pituitrin injections without any improvement in the condition. Repeated injections of increasing doses of histamin brought about a temporary desensitization which lasted for 5 weeks, after which the edema reappeared. Another series of histamin injections was given, and 11 months after the last injection there had been no reappearance of the swelling.

In view of the cases just reported on the favorable influence of histamin on states of physical allergy, we felt that such therapy might present some measure of potential value in the insulin-sensitive diabetic. We decided to study the effect of repeated injections of histamin on a patient who had been continuously sensitive to all types of commercial insulin for a period of 1 year.

Case Report. J. A., male, aged 58, had been diabetic for over 9 years, during the first 8 of which the condition was controlled by diet alone. In November, 1932, he had a sudden break in sugar tolerance, necessitating his return for treatment. He complained of weakness, weight loss, polyuria, polydipsia, sleeplessness, headaches, a voracious appetite and constipation. The physical examination disclosed nothing significant except evidences of wasting. The blood pressure was 146/90. He was excreting 2.5% sugar in the urine, a total of 25 gm. in 24 hours. His fasting blood sugar was 186 mg. His weight was 123 pounds; his height, 5 feet 3 inches. He was placed on a diet containing carbohydrate, 180 gm., protein, 60 gm., fat, 150 gm., having a caloric value of 2400 and containing 231 gm. of available glucose. He was given 10 units of Lilly insulin (U–40) b. i. d. At the end of a week he had gained 1½ pounds, his fasting blood sugar was 140 mg. per 100 cc. and the excretion of glucose in his urine was only a trace. Twelve days after insulin therapy was instituted he developed local reactions at the site of injection, characterized by redness, heat, swelling, induration, itching and pain. These reactions came on 6 to 8 hours after the injection and lasted about 36 hours. He was then ordered to take Lilly Special insulin (U–40) to which he reacted similarly. Intradermal skin tests were then performed with the following samples of insulin: (1) Lilly, (2) Lilly Special (prepared from beef pancreas only), (3) Lilly Hog, (4) Stearns, (5) Mulford and (6) Squibb. The local reactions were strongly positive and equal in all cases. As a result of this experience we found it necessary to stop the administration of insulin and treat him with dietetic measures. He was then placed on a diet containing carbohydrates, 125 gm., protein, 60 gm., fat, 200 gm., with a caloric value of 2500, and containing 181 gm.

of available glucose. On this diet he excreted 12 gm. of sugar in 24 hours, and his fasting blood sugar was 154 mg. On October 20, 1933, subcutaneous injections of histamin phosphate were started, beginning with 0.1 mg. and gradually increasing the dose until he was receiving 1 mg. per dose. Injections were given 3 times a week for 13 doses. For the first 10 days he continued to take insulin on those days on which he did not receive histamin. About 1 hour after taking the insulin he developed either local areas of induration at the site of injection, or generalized urticarial wheals and itching over the entire body. After the 4th injection of histamin insulin was stopped until after the 8th injection, when he received 1 mg. of histamin. The histamin was stopped, and insulin therapy instituted once more for a period of 1 week. During this time he developed local reactions at the site of injection, and although the reactions were much milder than those he formerly experienced, it was decided to stop the insulin and give him another series of histamin injections, starting with 0.5 mg. for 1 dose, and then giving 4 injections of 1 mg. each. The reactions to the histamin were characteristically uniform throughout the treatment, differing only in severity. At the site of injection he developed a local reaction which consisted of severe itching, wheal formation and surrounding erythema. There were generalized reactions of marked flushing of the face, headache, sweating of the face, paresthesias of the palms of the hands, dizziness, sneezing and depression of blood pressure.

After the last injection of histamin the patient was put on a diet containing carbohydrates, 170 gm., protein, 75 gm., fat, 140 gm., with a caloric value of 2240, and 10 units of insulin once a day. It is now 6 months since histamin was given, and he has been taking 15 units of insulin daily without any local reaction whatever.

Discussion. The rationale of the use of histamin as a therapeutic agent for desensitizing immunologically sensitive individuals is not clear to us. The rôle of histamin in immunology has been subjected to a considerable degree of investigation. Lewis and Grant,[8] in studying vascular reactions of the skin to injury, have produced evidence to indicate that the wheal resulting from stroking of the skin contains a histamin-like substance. Their theory is that histamin is locked up in the tissue cell and is suddenly released by skin injury. Histamin will similarly be liberated in response to scratching, pricking and heat. The reports of cases of physical allergy such as the development of localized edema of an extremity following immersion in cold water seems to fall into the category of factitious urticaria resulting from skin injury and resembles the experimental phenomena of Lewis and Grant. It would appear, on the face of it, that the edema fluid in these cases contains histamin-like substances, although there has been no experimental evidence to prove this point. How, under such circumstances, the repeated injections of histamin is beneficial in cases of physical allergy or factitious urticaria is difficult for us to understand. In spite of the difficulty in interpreting the therapeutic mode of its action, we have been struck with its beneficial effect in the treatment of physical allergy and, in our case, of insulin hypersensitiveness.

There seems to be every indication that the phenomenon of insulin hypersensitivity is an antigen-antibody reaction. The supporting

evidence for this concept is (1) that local passive transfer of sensitized serum has given positive results, and (2) that it takes approximately 8 to 10 days for the sensitivity to develop, closely resembling the incubation period of serum sickness. It is difficult to conceive that the sensitization arises from the complex protein molecule itself, because up to our present degree of understanding, crystalline insulin, from whatever source, seems to have the same type of chemical construction. In view of the fact that most patients obtain relief from these reactions by changing the commercial brand of insulin, it would appear that the guilty protein is not in the insulin molecule itself, but in the protein carried along through the various stages of so-called purification. As a matter of fact, the evidence that the insulin molecule is a protein has not been absolutely established, for evidence has been presented to show that the crystalline insulin of Abel is not the molecule of insulin itself but may be a crystal of protein to which the activated insulin has been adsorbed.[9]

Summary and Conclusions. 1. The incidence of local insulin hypersensitiveness has been discussed. In our collected series of 408 insulin-treated diabetics we found an incidence of 7.3%.

2. This phenomenon appears to be an antigen-antibody reaction.

3. Favorable therapeutic results have been obtained by means of insulin desensitization.

4. Our best and quickest therapeutic effect was produced by repeated injections of histamin phosphate. A case is reported.

NOTE.—We wish to express our appreciation to Eli Lilly and Company for their coöperation and assistance in this study.

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SIGNIFICANT ACTIVE PULMONARY TUBERCULOSIS IN THE APPARENTLY HEALTHY ADULT. A STUDY OF 141 CASES.

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IT is imperative to detect pulmonary tuberculosis in its earliest stage both for the most successful treatment of the patient and for the control of the disease from a public health standpoint. This

is fundamental and so generally accepted that amplification of this statement is unnecessary. How to attain this ideal is the question.

The purpose of this report is to record such an attempt with the results obtained to date. Before proceeding with the actual report, a few words of explanation are necessary. Prior to 1927, applicants for employment at the Home Office of the Metropolitan Life Insurance Company received an average careful and thorough physical examination before acceptance. Those persons admitting a history of a condition associated with pulmonary tuberculosis and those who presented unusual physical signs received a Roentgen ray examination of the chest. After appointment each Home Office employee received an annual physical examination and such laboratory examinations as were necessary. In spite of these precautions, it was not unusual to detect advanced pulmonary tuberculosis in an employee shortly after a negative physical examination. There were two possibilities to consider: (1) we might be dealing with a type of disease of rapid onset and progression or (2) our method of physical examination of the lungs had shortcomings. It was decided to attempt to determine where the truth lay. Admittedly, a routine Roentgen ray film of each individual at a pre-employment examination or annual examination would be the ideal method of recording the absence or presence of an evident pulmonary lesion. The expense of such a procedure was considered prohibitive unless proved necessary. As a substitute, fluoroscopes were installed and the entire medical staff was trained to make a fluoroscopic examination of the thorax in addition to the usual physical examination. The sole purpose of such an examination was to determine whether or not we were dealing with a healthy adult chest, or whether more intensive study by Roentgen ray was indicated. Our experience with the fluoroscopic examination, gained in the past 7 years, has convinced us that it is most important and we believe that no physical examination should be considered complete without either a Roentgen ray film or a fluoroscopic examination of the thorax. So much by way of introduction.

The points of particular interest in this report are:

A. The cases studied were adults with significant active pulmonary tuberculosis.

B. The group included an encouragingly large proportion of minimal cases.

C. The majority of the cases were detected before the patients became "ill."

D. The majority of cases were detected before physical signs were evident.

E. Positive sputum or positive guinea-pig were relatively numerous at some time during the period of treatment.

A. The diagnosis of pulmonary tuberculosis was confirmed on 131 (93%) at the Metropolitan Life Insurance Company Sanatorium

at Mount McGregor. The other 10 (7%) cases did not go to the Sanatorium and the diagnosis was established in a logical, orderly fashion by the Home Office Medical Division or outside agencies.

While the large majority of the cases were detected between the ages of 17 and 24, yet it is to be noted that 27 of the cases were over 25 at the time of initial diagnosis (see Table 1).

TABLE 1.—SEX AND AGE AT DIAGNOSIS ACCORDING TO THE REASON FOR TAKING THE ROENTGENOGRAM ON WHICH DIAGNOSIS WAS MADE.

Reason for taking Roentgenogram.	Males.				Females.			
	Total.	Age 17–19	Age 20–24	Age 25 and over.	Total.	Age 17–19	Age 20–24	Age 25 and over.
History	11	5	2	4	62	16	37	9
Fluoroscopic findings	10	1	6	3	49	6	34	9
Routine re-Roentgenogram	1	..	1	..	8	2	4	2
Total	22	6	9	7	119	24	75	20

B. Ninety-one (65%) were detected in the minimal stage; 42 (30%) in the moderately advanced; and 8 (5%) in the far-advanced stage. The proportion of minimal cases in this group admitted to our Sanatorium for treatment is about five times as great as the average admission rate of minimal cases reported by Hill and Williams in a survey of representative sanatoria made in 1929 (see Table 2).

TABLE 2.—STAGE AT DIAGNOSIS ACCORDING TO THE REASON FOR TAKING THE THE ROENTGENOGRAM ON WHICH THE DIAGNOSIS WAS MADE.

Reason for taking Roentgenogram.	Total.	Minimal.	Moderately advanced.	Far advanced.
History	73	44	23	6
Fluoroscopic findings	59	41	16	2
Routine re-Roentgenogram	9	6	3	
Total	141	91	42	8

C. It should be emphasized that in this entire group of patients there were only a very few who were toxic or would be considered as obviously "ill" from a clinical standpoint.

There were 47 (33%) who were symptom-free, and it was only after close questioning that 13 (9%) admitted fatigue only, 18 (13%) cough, or cough and expectoration alone, and 14 (10%) slight chest pain only. In other words, 92 (65%) were symptom-free or had only one symptom, not in itself pathognomonic (see Table 3).

D. Of the entire group of 141, only 59 (42%) had râles at either

the examination at the Home Office or on admission to the Sanatorium; 6 (4%) had evidence of pleurisy with effusion.

TABLE 3.—SYMPTOMS ELICITED AT HOME OFFICE AT TIME OF ROENTGENOGRAM OR AT EXAMINATION A FEW DAYS AFTER DIAGNOSIS WAS MADE; ACCORDING TO STAGE.

Symptoms.	Total.	Min.	M. A.	F. A.
No symptoms	47	37	9	1
Fatigue only	13	10	3	—
Cough only	18	8	6	4
Chest pain only	14	10	4	—
Hemoptysis only	4	2	1	1
Two or more symptoms	45	24	19	2
Total	141	91	42	8

There were 63 who had lost 3 pounds or more; 27 who had gained 3 pounds or more; and 51 whose weight has been stationary (±2 pounds) within the year prior to establishing the diagnosis (see Table 4).

TABLE 4.—WEIGHT CHANGES WITHIN 1 YEAR PRIOR TO DIAGNOSIS; ACCORDING TO STAGE OF DISEASE.

Stage	Total.	Loss 6 pounds or more.	Loss 3–5 pounds.	Stationary + or − 2 pounds.	Gain 3–5 pounds.	Gain 6 pounds or more.
Min.	91	25	16	32	13	5
M. A.	42	10	9	17	2	4
F. A.	8	1	2	2	2	1
Total	141	36	27	51	17	10

E. Of the 131 cases who went to the Sanatorium, 25 had a positive sputum, 12 a positive guinea-pig, and 4 had a positive sputum and positive guinea pig at some time during the course of their treatment, and 90 had negative laboratory reports. Thirty-one per cent, then, had either a positive sputum or a positive guinea-pig at some time during their treatment.

TABLE 5.—LABORATORY FINDINGS BY STAGE AT TIME OF DIAGNOSIS; 131 PATIENTS WHO WENT TO THE METROPOLITAN LIFE INSURANCE COMPANY SANATORIUM.

Stage.	Cases.	Negative laboratory findings.	Sputum positive.	Guinea-pig positive.
Min.	83	72	8 (3)	6 (3)
M. A.	41	16	17 (1)	9 (1)
F. A.	7	2	4	1
Total	131	90	29 (4)	16 (4)

Cases in parentheses had positive sputum and positive guinea-pig.

Of those who went to the Sanatorium, 73 first had Roentgen ray examinations because of a slightly suggestive history; 28 (38%) of them had a positive sputum or guinea-pig test or both.

Of those 68 who had Roentgen ray examinations because of fluoroscopic findings or as a routine reëxamination 13 (19%) had positive sputum or guinea-pig test or both during treatment (see Table 5).

It is interesting to note that there were only 26 known or questionable cases of contact.

Conclusion. It is possible to detect cases of active pulmonary tuberculosis roentgenologically before symptoms and physical signs become established.

I wish to express my appreciation to Mrs. Margaret G. Stephens and Miss Margaret Wichmann for their part in the preparation of this paper.

THE TUBERCULIN REACTION IN RHEUMATIC FEVER.

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(From the Department of Pediatrics, The Jewish Hospital of Brooklyn, Dr. Benjamin Kramer, Pediatrician-in-Chief.)

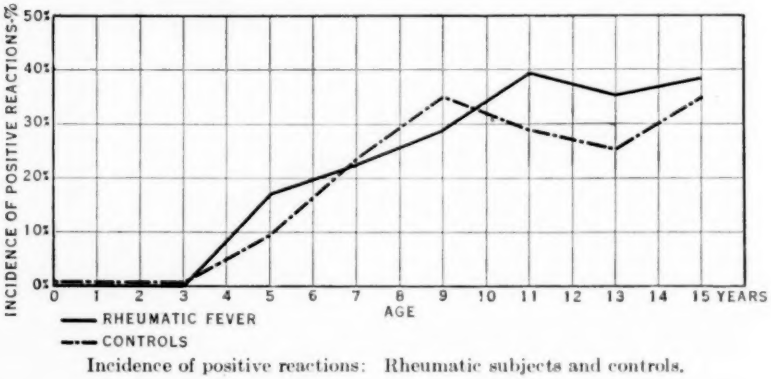
The similarities between rheumatic fever and tuberculosis have been pointed out for many years. The two diseases have been compared clinically,[1,15] epidemiologically,[16] pathologically[11] and immunologically.[11] More recently the similarities in the skin manifestations of both diseases have been emphasized.[17,20] New interest has been aroused in the whole subject by the work of Liebermeister,[20] Reitter and Löwenstein.[21,28] The latter found as high as 70% positive cultures for tubercle bacilli in blood of patients with rheumatic fever.

With these interesting considerations as a background, we thought it would be of interest to study the nature of the tuberculin reaction in rheumatic fever. From an earlier investigation made by Sulzberger and Feit,[29] on a group of 20 children with rheumatic fever in the quiescent stage, and with cardiac decompensation, it appeared that patients with this form of infection were less sensitive to tuberculin than the normal. After discussion with Dr. Sulzberger we agreed that, in order to determine whether or not the reaction to tuberculin in rheumatic fever subjects was altered, a more comprehensive study was essential.

In our series we studied the reaction of 245 patients with rheumatic fever. The group consisted of children between the ages of 2 to 15 years. During the active phase of the disease 157 cases were tested, 88 during the quiescent stage and 35 tested during both periods. Inactive as well as active cases were included in order to determine whether or not the degree of tuberculin sensitivity might be influenced by the activity of the infection. The series also

included 44 cases of chorea, 16 of which were retested after the choreiform movements had completely subsided. The studies were carried out on cases of rheumatic fever admitted to the Pediatric Division of the Jewish Hospital of Brooklyn. The active series included patients with joint, nervous system, cardiac and skin manifestations, either individually or in combination. Those with cardiac disease were in the majority of instances classified as II *A* II *B* (American Heart Association classification). Only patients without symptoms or signs of activity and with a sedimentation time of over 2 hours (Linzenmeir method) were considered inactive.[30]

The initial test was made with 0.1 mg. of Old Tuberculin (N. Y. City Board of Health) injected intradermally (Mantoux).



Incidence of positive reactions: Rheumatic subjects and controls.

When this first injection produced no reaction, the patients were retested with 1 mg. and 5 mg. (respectively 0.1 cc. of a 1 to 1000 dilution, 0.1 cc. of a 1 to 100 and 0.1 cc. of a 1 to 20 dil.). Sterile carbosaline was used as a control. Patients were observed for local, general and focal reactions.

As the control group 273 patients of comparable age were employed. The controls were selected from admissions to the service suffering from various febrile and afebrile conditions not including rheumatic fever or tuberculosis. Moribund patients, cases of sepsis or of questionable diagnosis were also excluded. It was felt that such controls would be more exact than healthy school children, since Hart[31] and others have shown that most febrile conditions tend to lower the tuberculin reactivity to some degree. It was reasonable to assume that rheumatic fever would probably exert the same non-specific effect as other infections, and in comparison with a healthy group would, therefore, probably show a lowered incidence of tuberculin reactivity. By using hospital patients, both febrile and afebrile, as in the rheumatic group, such a source of error was obviated. The following observations were made:

1. The total incidence of positive tuberculin reactions in rheumatic fever subjects was found to be approximately the same as in the non-rheumatics.

(*a*) Total incidence of positives in rheumatic fever, 26.9%.

(*b*) Total incidence of positives in control group, 24.4%.

2. The incidence of positive reactions for each age group was approximately the same in the rheumatics and the non-rheumatics (Table 1).

TABLE 1.—POSITIVE TUBERCULIN TESTS IN RHEUMATIC FEVER.

Age group.	Rheumatic fever.		Controls.	
	Number tested.	Per cent positive.	Number tested.	Per cent positive.
2 to 3	6	0	10	0
4 to 5	24	16.6	21	9.5
6 to 7	32	22.3	56	23.4
8 to 9	52	28.8	64	34.8
10 to 11	55	39.3	43	29.1
12 to 13	61	35.2	62	25.6
14 to 15	15	38.3	17	34.3
Total and average %	245	25.7	273	22.3
	Av. age = 9.41 yrs.		Av. age = 9.27 + yrs.	

3. The rise in incidence of positive reactions with increasing age in the rheumatic fever series closely paralleled that of the control group (see graph).

4. The reaction to tuberculin was the same in both phases of the disease (active and inactive).

(*a*) Positive incidence in active group, 26.6%.

(*b*) Positive incidence in the inactive group, 28.5%.

(*c*) In 35 cases tested during the active and inactive phases of the disease it was shown that:

Twenty-two cases negative during the active stage remained negative in the inactive stage.

Eight cases positive during the active stage remained positive in the inactive stage.

Five cases negative during the active stage were positive when retested during an inactive phase; 4 of these were retested after a period of 1 year and 1 was retested after an interval of 2 years. This alteration in the reaction in the last group can be accounted for by the well-known rise in incidence of infection with increasing age as the opportunity for contact with tuberculosis increases.

(*d*) Four patients who were previously negative and were retested during a recurrence of active symptoms remained negative.

5. The incidence of positive tuberculin reactions in the chorea group was 22.2%, almost identical with that of the control group. The reaction to tuberculin did not change in any of the 16 cases retested after cessation of the choreiform movements.

6. No systemic effect or focal flare up following the injection of

tuberculin, such as described by Reitter and Löwenstein was observed in any patient, even when the local response was markedly positive.

Comment. The reliability of the tuberculin test as method of determining tuberculous infection, with very few exceptions, is well enough established. The notable exceptions occur:

1. During the interval between infection with tuberculosis and the development of hypersensitivity.
2. During tuberculin therapy.
3. In conditions with negative anergy, *e. g.*, cachexia, moribund states, miliary tuberculosis, postexanthemata, especially measles.
4. In conditions with positive anergy, *i. e.*, in certain skin and other diseases, *e. g.*, sarcoids, lupus pernio, lupus miliaris faciei, some case of papulonecrotic tuberculids and erythema induratum and in osteitis tuberculosa cystica of Jüngling.[34,35,36] (For English ref. see Jadassohn,[32] and Sulzberger and Wise.[33])

Two types of anergy (positive and negative) are now recognized in view of the work of Jadassohn, Pickert and Löwenstein,[37] Jadassohn,[38] Martenstein and Noll,[39] and others.[40]

Negative anergy can again be of two sorts:

(*a*) One in which the power to react to tuberculin is diminished or lost as result of an exhausted state.

(*b*) Or because there has been no opportunity for the formation of hypersensitivity (as when infection has never taken place).

Positive or specific anergy, on the other hand, occurs in certain forms of tuberculosis with a relatively benign course, notably sarcoids of skin, lungs and bone (osteitis cystica).

In these patients the altered reaction to tuberculin, *i. e.*, the diminished sensitivity, has been attributed to some degree to the presence of certain substances in the blood serum and in the tissue fluids expressed from the lesions. For these fluids, when obtained from patients with a positive anergy, and when mixed with tuberculin *in vitro* in certain proportions, are found to counteract the effects of tuberculin. These substances have been designated as anticutines by Pickert and Löwenstein.[37]

Because of the existence of positive anergy in certain forms of disease, known to be due to the tubercle bacillus, a marked decrease of sensitivity to tuberculin when regularly encountered might speak in favor of tuberculosis. However, we found no alteration in the tuberculin reaction in our patients either in the direction of hyperergy nor anergy, and may thus state that we could demonstrate no response speaking in favor of rheumatic fever being a tuberculous disease. For it seems reasonable to assume that if rheumatic fever were a tuberculous condition, as claimed by Reitter and Löwenstein, this would have been reflected in the abnormal (hypoergic or hyperergic) response to tuberculin.

Conclusions. 1. A study made of the tuberculin reaction (quantitative Mantoux) in 245 cases of rheumatic fever in childhood shows that there is no divergence from the normal in the tuberculin reactivity in this group.

2. This fact constitutes evidence against an etiologic relationship between rheumatic fever and tuberculosis.

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SEPTICEMIA: A METHOD OF TREATMENT.

REPORT OF ONE HUNDRED CASES.

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THE diagnosis of septicemia in the cases included in this report rested on two facts: (1) That the patients presented the symptoms characteristic of the disease; and (2) that blood cultures were positive. A streptococcus or staphylococcus was recovered from the blood of each patient. When considered advisable, blood cultures were repeated and confirmed.

The cases under review cover a period of 8 years and are unselected. Of the 100 patients treated, 85 recovered, a mortality rate of 15%. Excluding the 5 cases of subacute bacterial endocarditis, all of which proved fatal, the mortality rate was 10.5%.

Procedure. Numerous strains of streptococci and staphylococci are recovered from patients with septicemia or from patients with pyemic foci resulting from infection with these bacteria. The microörganisms are cultured in serum broth and a vaccine prepared. A number of rabbits are selected and inoculated with a heavy suspension of the vaccine. Vaccine is administered to the rabbit when 6 months old and the inoculations continued twice weekly throughout the useful life of the rabbit, using numerous strains of streptococci and staphylococci. The subcutaneous and intravenous route are both employed. When one of these animals is two years of age it is considered suitable for the immediate purpose in view. I keep 25 rabbits continuously immunized.

When a positive culture is obtained from a patient showing symptoms of septicemia, a vaccine of the microörganism is prepared as rapidly as possible (generally within 24 hours), and this vaccine is inoculated into a series of the immunized rabbits. On the following day, from 6 to 10 cc. of blood are withdrawn by means of a vacuum tube from the heart of one of these rabbits, the blood is allowed to clot, the serum is removed, tested for sterility, and the patient is then inoculated subcutaneously or intramuscularly with this serum. Inoculations with the vaccine of the causative organism are continued daily with the series of rabbits already immunized and which have been selected for use in the particular case under treatment. If necessary the serum from the blood of these rabbits in rotation is administered to the patient on successive days.

The patient's blood is directly matched for a compatible donor. It is of advantage to have this procedure completed on the earliest indication that the case may prove to be one of septicemia. The suitable donor reports to the laboratory and from 60 to 100 cc. of blood are withdrawn into a large vacuum tube. The blood is allowed to clot at room temperature, and subsequently placed in the ice chest for 12 to 18 hours. The serum is removed and the patient is transfused with this serum. If considered necessary, this procedure is also carried out daily, in which case it may be advisable to have more than 1 donor. As a rule, I have administered the human serum on alternate days. The average number of

combined treatments administered to the patients was 4, the greatest number administered to any single patient, 10.

No drugs were given during the course of the treatment. On occasion, whisky was prescribed as a stimulant and then sparingly. The patient was encouraged to partake of a fairly liberal diet.

Serum treatment was instituted on the average on the 6th day following the initial symptoms; the earlier administration was on the 3d day, the most delayed on the 16th day. The first treatment with serum administered to a patient with subacute bacterial endocarditis was 6 weeks subsequent to the initial symptoms.

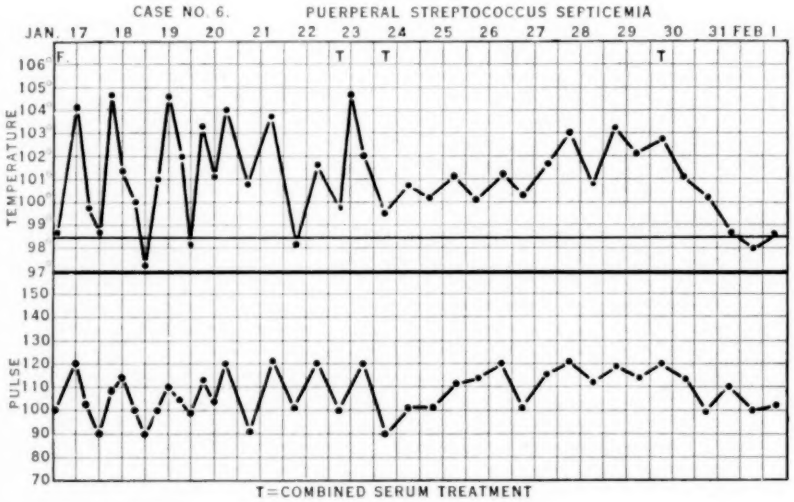
CASE NO. 6.
PUERPERAL STREPTOCOCCUS SEPTICEMIA
JAN. 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 FEB 1
F.
T T T
TEMPERATURE
106 105 104 103 102 101 100 99 98 97
PULSE
150 140 130 120 110 100 90 80 70
T=COMBINED SERUM TREATMENT

CHART I.

Clinical Notes. Frequently following the administration of the serum a definite change is noted in the character of the temperature and pulse (see charts). The patient's general condition improves and foci of infection give definite evidence of localizing. Blood cultures rapidly became sterile in the cases that recovered and remained positive in those in which there was a fatal termination, with the exception of 2 cases. One of the latter was a case of endocarditis, mentioned later, the other a young girl who had apparently recovered from the septicemia but subsequently died following the rupture into the bronchi of a lung abscess.

Of the 100 patients, 90% developed a temperature of 104° F. or over; 92% had been characterized by the sudden elevations and remissions of fever associated with septicemia. The character of the temperature range did not prove to be of prognostic value; the percentage of recoveries was as high in those patients with the greatest elevation of temperature as in those with the least. The highest temperature recorded, 108° F., occurred in a patient with

a streptococcal septicemia of puerperal origin; this unusual temperature was checked; the patient recovered.

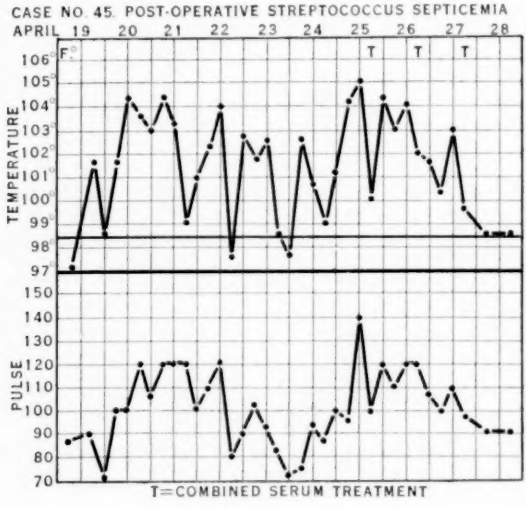
CASE NO. 45. POST-OPERATIVE STREPTOCOCCUS SEPTICEMIA
APRIL 19 20 21 22 23 24 25 26 27 28
F°
T T T
TEMPERATURE
106° 105° 104° 103° 102° 101° 100° 99° 98° 97°
PULSE
150 140 130 120 110 100 90 80 70
T=COMBINED SERUM TREATMENT

CHART II.

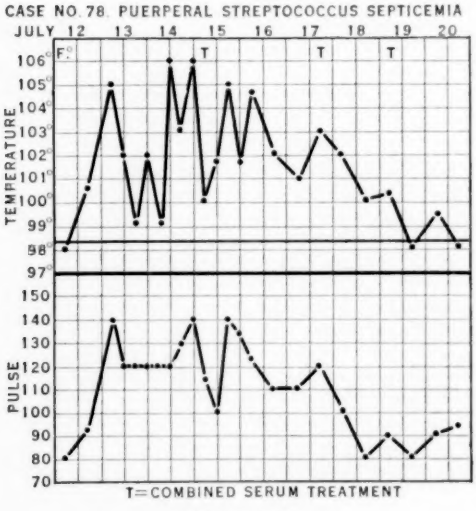
CASE NO. 78. PUERPERAL STREPTOCOCCUS SEPTICEMIA
JULY 12 13 14 15 16 17 18 19 20
F°
T T T
TEMPERATURE
106° 105° 104° 103° 102° 101° 100° 99° 98° 97°
PULSE
150 140 130 120 110 100 90 80 70
T=COMBINED SERUM TREATMENT

CHART III.

The pulse rate, as a rule, followed the temperature range, although in several cases it remained relatively high compared to the temperature.

Meningitis proved a serious complication in 8 patients; 6 died and 2 completely recovered. In each of these 8, symptoms of meningitis were present before serum therapy was instituted and the microörganism was recovered from the spinal fluid in 7 of them.

TABLE 1.—REPORT OF CASES (RECOVERY).

Source.	No.	Age aver.	Age range.	Sex.	Blood culture.	Complications.
Puerperal	24	26	18–42	..	S. hemol., 12; strep., 12	Abscesses, 8; nephritis, 4; phlebitis, 2; total, 16.
Wounds	17	30	9–60	M 12 F 5	S. hemol., 11; strep., 2; staph., 2	Cellulitis, 8; met. abscesses, 7; gangrene toes, 1.
Mastoid	14	19	4–38	M 5 F 9	S. hemol., 8; strep., 5; staph., 1	Met. abscesses, 2; mastitis, nephritis, dislocated hip, bronchitis, meningitis.
Septic throat	12	26	6–52	M 9 F 3	S. hemol., 8; strep., 3; staph., 1	Endocarditis, 3; meningitis; nephritis, 2; panophthalmitis; met. abscess.
Postop. and tooth extraction	9	24	9–46	M 5 F 4	S. hemol., 6; strep., 2; staph., 1	Abscesses, 4; arthritis, cellulitis.
Miscellaneous	9	15	$\frac{1}{12}$–44	M 9	S. hemol., 2; strep., 3; staph., 4	Osteomyelitis with met. abscesses, 4; abscesses (thigh, perinephritic, cervical), septic lung, navel infection.

S. hemol., streptococcus hemolyticus; strep., streptococcus; staph., staphylococcus; met. abscesses, metastatic abscesses.

TABLE 2.—REPORT OF CASES (FATAL).

Case No.	Age.	Sex.	Source.	Blood culture.	Complication.
39	39	F	Puerperal	S. hemol.	Staph.
10	47	F	Burn of arm	S. hemol.	B. pyocyaneus.
68	9	M	Wound of leg	Strep.	Meningitis.
70	50	M	Wound of foot	S. hemol.	Meningitis.
83	50	M	Wound of foot	S. hemol.	Pneumonia.
89	14	F	Mastoid	Strep.	Abscess lung.
88	52	F	Septic throat	Strep.	Meningitis.
44	46	M	Sinus operation	S. hemol.	Meningitis.
25	14	M	Osteomyelitis	Staph.	Meningitis.
48	35	F	Abscess of neck	S. hemol.	Meningitis.
65	45	M	Subacute bacterial endocarditis	Strep.	Staph.
79	24	F	Subacute bacterial endocarditis	S. viridans	Emboli.
80	42	F	Subacute bacterial endocarditis	S. viridans	Emboli.
81	43	F	Subacute bacterial endocarditis	S. hemol.	Pneumonia.
91	35	F	Subacute bacterial endocarditis	Strep.	Emboli.

S. hemol., streptococcus hemolyticus; s. viridans, streptococcus viridans; met. abscesses, metastatic abscesses; staph., staphylococcus.

During the later stages of the disease in 3 cases arising from a primary streptococcus infection, a secondary invader appeared in the blood stream, in 2 cases a staphylococcus and in the third the Bacillus pyocyaneus. In each of these patients the secondary invader, previous to its appearance in the blood stream, had been

noted in cultures made from an open lesion. Each of these 3 cases of double infection proved fatal.

No untoward effects associated with the inoculation of the animal serum were noted. On 2 occasions during the first transfusion of the human serum, although it was obtained from a supposedly compatible donor, the patient developed anaphylactic symptoms. About 3 cc. of the serum had been given when the symptoms appeared; the transfusion was discontinued; another donor was obtained for each of these patients and no reaction occurred following the administration of the second donor's serum.

A definite localizing and rapid healing of secondary foci occurred in the patients who showed improvement following the treatment and in whom metastatic abscesses had previously developed.

Comment. The experimental evidence in support of and the reason for this method of treatment I have submitted in papers previously published.[1,2,3] As a rule, in septicemia a rapid fall in the complement power of the patient's blood occurs; transfusion of normal human serum reactivates this property. Serum is used in preference to whole-blood transfusion because the cellular elements of the donor's blood apparently lower the patient's complement.

The rabbits immunized as previously described show a high degree of resistance to experimental infection. Also, as a rule, the rabbit serum contains specific antibodies for the majority of the strains of streptococci and staphylococci recovered from the patients with septicemia. These were demonstrated by the agglutination, precipitation and bacteriolytic reactions. On occasion, however, a streptococcus is isolated from the blood stream of a patient, for which streptococcus these immune properties of the animal serum are present in but a slight degree. In such a case it is necessary to stimulate the formation of the antibodies in the rabbits by repeated inoculations with the specific organism.

In our experience withdrawal of the blood from the heart of a rabbit while anesthetized does it no harm.

The 5 cases of subacute bacterial endocarditis proved fatal. There is a question whether such cases should be classed with septicemia. The focus in the heart is the grave pathologic condition to be considered; the intermittent bacteriemia associated with this lesion is secondary. An invasion of the blood stream by a streptococcus or staphylococcus giving rise to the acute symptoms of septicemia differs from the slowly progressive bacterial invasion, so graphically described by Boyd,[4] of a previously damaged heart. The complement power of the blood of the patients with subacute bacterial endocarditis remained constantly at extremely low levels. Following the initiation of the treatment, an apparent improvement occurred in the general condition of these latter patients. In 1 case the temperature returned to the normal level, the blood culture became sterile and the patient who had been confined to bed for

2 months was able to move about; however, the clinical evidence indicated that the heart was seriously damaged and the patient died suddenly 1 month later following slight extra physical exertion. The added injury resulting from the bacterial invasion of an already damaged endocardium, particular to subacute bacterial endocarditis, is evidently beyond the body's resources for efficient mechanical repair.

A diagnosis of the complication of acute bacterial endocarditis was made in 3 of the patients, all of whom recovered and have since remained in good health.

In septicemia prompt action is important. The early recognition of the nature of the case and the immediate application of a definite method of treatment may prove the deciding factor for a fortunate outcome.

The evaluation of the special laboratory procedures that may be undertaken in the treatment of septicemia (Kolmer[5]) presents many difficulties. Patients with the disease may, and do on occasion, recover when left to their own resources. The result in any single case depends upon the nature of the microörganism and the resistance of the host, both of which factors are variable and interdependent. The argument may be advanced that, in any series of cases such as are recorded here, the fortunate circumstance of low virulence and high resistance may play an important part in the results noted. Experimental evidence gives little aid in elucidating this problem, since septicemia in the animal varies considerably from that in man. The question of controls arises, but an accurate system of human controls is difficult to attain.

The records of the patients with septicemia from whom a positive blood culture had been obtained in our laboratory previous to the time covered by this report showed that the mortality rate was over 85%; similar statistics were obtained from a large hospital in Winnipeg. Accurate statistics on the mortality rates in septicemia resulting from a streptococcus or staphylococcus invasion originating from foci in various tissues are difficult to secure. Evidently the mortality rate in such cases is much higher than we have been content to believe.

Summary. A method is described for the treatment of septicemia by inoculation of a specific antiserum and by transfusion of normal human blood serum. A brief report of 100 cases is submitted: 85 of the patients recovered. Excluding the 5 cases of subacute bacterial endocarditis, all fatal, the mortality rate of the other 95 cases was 10.5%.

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THE VALUE OF THE CUTANEOUS HISTAMIN REACTION IN THE PROGNOSIS OF PEDAL LESIONS IN DIABETES MELLITUS.

AFTER-HISTORIES OF 89 PATIENTS FOR FIVE YEARS.

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SOMEWHAT over 5 years ago an investigation was undertaken to discover whether aid in the diagnosis and prognosis of peripheral vascular disease could be secured by the reaction of the skin to histamin.[1,2] It was known that this response could be greatly changed by experimental obstruction of the circulation,[3] and it soon became evident that abnormal histamin reactions were almost invariably associated with the other manifestations of diminished circulation in the extremities. Therefore, it has been generally agreed that the skin histamin reaction affords a simple means of roughly measuring this circulation.[1,2,4,5,6,7]

The question then presented itself whether this simple test of circulatory efficiency could be used to detect those patients who, suffering from a disease frequently accompanied by gangrene, were in especial danger of this complication. Therefore, in 1928–29, we elicited the histamin reaction on the lower extremities of 100 consecutive cases of diabetes mellitus with the intention of keeping in touch with these patients for a prolonged period.[2] Somewhat over 5 years has elapsed and it has been possible to secure recent information concerning 89 of them. The results secured 5 years ago may now be compared with the outcome and the prognostic value of the cutaneous histamin response determined.

The patients with marked impairment of this reaction on their feet not only have developed a high incidence of serious trouble with their feet, but also have had a higher mortality than those with normal responses. No case with a normal response to histamin developed gangrene, persistent infections, ulceration, or intermittent claudication during the subsequent 5 years. The value of the histamin reaction, in predicting the likelihood of trouble with the feet in diabetes, seems to have been clearly demonstrated.

Method. Almost half the living patients were still attending the outpatient department of this or neighboring hospitals. Those dwelling in the city were seen in the clinic or at their homes. Information about the others was obtained by sending a questionnaire to their physicians, whose coöperation made the study possible. The visiting was performed by Miss Mary Pollock, of the Social Service Department, who also supervised

the other means of securing information. A large part of the expense was borne by the Civil Works Administration.

The normal response of the skin, to a minute amount of a 1 to 1000 solution of histamin acid phosphate pricked into it, is identical with that which follows a mosquito bite. It consists of a red spot, soon succeeded by a wheal, and surrounded by a flare. It is accompanied by itching. In normal persons all these features are manifest within five minutes. The technique of eliciting this response has been described.[1,2] When the circulation is abnormal the appearance of the wheal and flare may be delayed, or they may not appear at all, the response consisting of the spot only, or of nothing visible. For convenience of expression the normal reaction, complete within 5 minutes in both foot and knee will be spoken of as Grade I. A reaction on the foot lacking wheal or flare, or both, at the end of 5 minutes, but complete within 10 minutes, the reaction above the knee being normal, will be referred to as Grade II. A reaction on the foot failing to become complete within 10 minutes, that above the knee being normal, will be called Grade III.

TABLE 1.—CLINICAL COURSE OF 89 PATIENTS TESTED BY CUTANEOUS HISTAMIN REACTION 5 YEARS BEFORE.

Condition of circulation of feet 5 years ago.	No. of cases followed 5 years or until death.	No. who had lesions of feet when tested 5 years ago.	Died during 5-year period.	Survivors for 5 years.	No. who survived 5 years without serious trouble with feet.	Nature of trouble developing before death or within 5 yrs.; lesions present at time of original test not included; No. of patients who developed symptoms given below.			No. of patients requiring amputation.	No. of admissions to hospital wards for trouble with feet.
						Prolonged pain without other manifestations.	Chronic infections and ulcers without gangrene.	Gangrene.		
Normal histamin reactions normal	26	0	7	19	19	0	0	0	0	0
Slightly diminished histamin reactions Grade II	31	1	8	23	19	4	0	0	0	0
Markedly impaired histamin reactions Grade III	32	7	18	14	5	6	4	4	2	10

Results. In Table 1 a summary of the results has been given. The 89 patients have been grouped according to the grade of the histamin reactions obtained 5 years before. When the response on the 2 feet differed, the more abnormal has been used to classify the case. No case with normal (Grade I) reactions has had any serious trouble with the feet during the intervening period. Those with slightly diminished (Grade II) reactions have likewise had no serious trouble. Persistent pain in the feet, not typical of peripheral vascular disease, and not definitely to be assigned to any other

cause, was reported by 4 of them. This may indicate future trouble, but nothing of any gravity has supervened during the 5 years. The one exception to this statement was the case of E. A., who had a small patch of gangrene when tested 5 years ago and who died of embolism during the next few days. Therefore, it appears evident that, if the response of the skin of the feet to histamin is complete within 5 minutes, serious trouble with the feet need not be feared. If the reaction is complete within 10 minutes such trouble should not be expected.

But the situation is far different in the remaining group, those who had a highly abnormal response to histamin on their feet. Only 14 of the original 34 survived the 5-year period, only 5 of these survivors have avoided serious trouble with their feet. The following are brief reports of the more serious cases which I have been able to follow personally.

Case Abstracts. Case 1.—J. R., a woman, aged 67, has been diabetic since 1919, and is now on insulin. In 1928, she had a Grade III histamin reaction on both feet, no pulsation in the vessels of the feet and no color changes. The superficial vessels were moderately sclerotic. She had no serious trouble with her feet until 1930. Then the right foot began to pain and she sought admission. The foot was cold and discolored about the heel. Rest and diabetic control relieved the symptoms and she was discharged. Six months later (1931) she noted an ulcer on the 5th right toe. Six weeks of care by her doctor failed to heal it. It became increasingly painful and she again sought admission. Examination showed a necrotic lesion at the right heel, another at the right 5th toe and the right great toe was swollen, tender and painful. She remained in the hospital 3 months, during which conservative measures made but little progress. She declined amputation and was sent home with the lesions unhealed. She is still living (1934).

Case 2.—J. J., a man, aged 57, has been diabetic since 1919. No insulin until first admission. He had a Grade III reaction on both feet when tested in 1929. At this time the dorsalis pedis pulses were palpable but weak. No pulse could be felt in the posterior tibial arteries. No color changes were observed. His feet gave him no trouble until 1931, when he developed a number of ulcers which healed under treatment by his doctor. In February, 1933, the left foot became painful, then discolored, and he sought admission. Examination showed black superficial gangrenous plaques over the first metatarsal phalangeal joint, on the ball of the great toe and between 2d and 3d toes. The gangrene spread rapidly. Amputation was performed at midleg. Convalescence was uneventful. He is still living.

Case 3.—L. B., aged 57, known to have diabetes since 1913, had Grade III reactions on both feet when admitted with an ulcer on the *right* middle toe in 1929. The left dorsalis pedis pulse was strong, the right and the posterior tibial pulses could not be felt. No abnormal color was noted on the left foot. The ulcer healed under conservative measures. She was readmitted 1 year later (1930), with a superficial gangrenous spot on the *left* great toe. Conservative measures were again successful. She was readmitted in 1932, but not because of trouble with her feet. She died after an accident later in that year.

Case 4.—R. H., aged 50, known to have diabetes since 1925, had a Grade III histamin reaction on both feet in 1929. The pulse could be felt

in the dorsalis pedis and posterior tibial arteries. No abnormal color was observed. She had no trouble with her limbs until 1933, when after an apparently insignificant scratch the outside of the right foot became red, hot, swollen and painful and the redness rapidly extended up to the knee accompanied by burning and itching. She was admitted to the hospital and the infection subsided rapidly under hot wet dressings. Three months later she had a very similar infection, again requiring admission. This also subsided, to recur 3 times more at intervals of about 2 months, each attack requiring hospitalization. She is in the hospital at the time of writing (1934). Diagnosis, recurrent cellulitis.

Case 5.—Another man, not in the original group of 100 cases, shows a similar outcome. C. W., aged 58, with mild diabetes, diagnosed in 1931, was tested in that year when he came to the hospital because of an ulcer in his *left* foot. The *right* foot had caused him no trouble but both feet showed Grade III histamin reactions at this time. No pulse could be palpated in the vessels of either foot. When dependent, rubor extended on to the dorsum of the left foot but was confined to the toes on the right. The lesion healed in the thermoregulated cradle.[8] Two years later he was readmitted with ulcers on the *left* great toe and right heel. They again healed under conservative measures. In 1934, he was readmitted with a large gangrenous plaque under the *right* internal malcolus, and small ulcers on the right heel and great toe. The small ulcers healed but the gangrene spread. Amputation was performed above the knee. Thus a Grade III histamin reaction on the right foot was followed by gangrene 3 years later.

I am dependent on other physicians for reports of certain other cases in this group. A. M., with Grade III reactions on both feet in 1929, has had cramp-like pains in the legs since 1932. More recently she has had a succession of infections in the legs diagnosed recurrent phlebitis. These have not required hospitalization. E. M., who had Grade III reactions in 1929, had painful feet with chronic ulcerations before her death in 1933. A. G., with similar reactions in 1929, constantly complains of painful and swollen feet.

Discussion. In the preceding discussion histamin reactions have been classified as abnormal when either wheal or flare failed to appear. Obstruction of the circulation, whether pathologic or experimental, affects both together. In some cases, however, a good wheal is not accompanied by a flare, a condition which occurs when the peripheral nerves have degenerated.[3] Before this condition is diagnosed every effort must be made to bring out the flare by allowing the part to hang down or causing venous engorgement by a blood pressure cuff inflated to 30 mm. Hg. Because of the ease of determining its presence, and because it is independent of the nerve supply, the wheal is clearly more important than the flare in estimating the peripheral circulation. Therefore, we have continued to introduce the histamin by placing a drop on the skin and pricking the skin through the drop with a sharp needle. The intracutaneous injection of histamin, preferred by some clinics,[4] raises a wheal mechanically, and thus confuses the estimate of the histamin wheal. However, in the great majority of instances, either technique suffices.

The difference in mortality in the different groups, classified according to the histamin reaction alone (Table 1) deserves discussion. The group with markedly impaired histamin reactions has a mortality rate over twice that of the more normal groups. But the cases in this group averaged 55 years of age in 1929, those in the more normal groups averaged 44 years. In the older group more deaths are to be expected during a 5-year period. When these data are studied in the light of a standard mortality table, it is found that the difference in mortality between the groups is not greater than is to be expected at such different ages.* The histamin response gives no better indication of life expectancy in diabetes than the age of the patient.

We had hoped to obtain information concerning the relation between histamin response and the permissible level of amputation, but we have been able to secure very little data. We had anticipated[2] that it would be proper to amputate at a level where the histamin reaction was normal, dangerous to amputate where it was abnormal. In support of this concept may be cited 3 successful midleg amputations for diabetic gangrene when the histamin response was normal and 2 midleg amputations which failed, requiring reamputation at a higher level, when the reaction at the initial level was abnormal. But with the development of new methods, and an increasing interest in conservative procedures in recent years, we have seen a number of successful amputations of toes at levels where the histamin reaction was highly abnormal. Whether this can be accomplished without a special technique to overcome vascular spasm[8] and increase the circulation,[9] we do not know.

Observation of the cutaneous response to histamin and of the pulse in the superficial arteries permits the division of the cases into several groups, according to the location of the disease in small or large vessels, and the amount of vascular compensation.[2] It is now possible to study the outcome of the cases which, in 1929, fell into two especially interesting groups:

1. Lesions chiefly in the minute vessels (dorsalis pedis pulse strong, histamin reaction markedly impaired, Grade III). There were 8 cases in this group in 1929. Six of them did not survive the 5 years, a surprising mortality, not to be accounted for by their age, which averaged 47 in 1929. However, none of them are known to have developed serious trouble with their feet. The primary causes of death assigned by the attending physicians were heart disease (2 cases), diabetes (2 cases), nephritis and carcinoma. This heavy mortality defeated our purpose of discovering whether this condition predisposed to serious pedal lesions.

* I am indebted to Dr. L. I. Dublin for instructions as to how to compare a difference in mortality between groups of different ages on the basis of a standard mortality table.

2. Lesion in the large vessels without compensation (dorsalis pedis pulse absent, histamin reaction, Grade III). Thirteen of these cases have been followed; 8 are now dead; 6 had or developed frank gangrene. Only 1 survives without having had serious trouble with the feet during the 5-year period. The serious prognostic significance of this situation is evident.

It is of interest to compare the prognostic value of the histamin reaction with that of the most valuable single physical sign, pulsation in the dorsalis pedis artery. In Table 2 this comparison has been made on the basis of the cases surviving 5 years. In Table 3 a more exact method has been employed. The total number of years the patients in each group were exposed to risk of gangrene has been calculated. Thus, the cases surviving the 5-year period of observation were exposed for 5 years, but patients dying before 5 years had elapsed were exposed only during the period between the beginning of observation and their deaths. The ratio of the years exposed in each group to the number of patients developing serious lesions gives an index of the prognostic value. In compiling Table 3, lesions present when the tests were made, in 1929, have been disregarded, only lesions developing afterward having been included.

TABLE 2.—COMPARISON OF PROGNOSTIC VALUE OF HISTAMIN REACTION AND DORSALIS PEDIS PULSATION.

Condition 5 years ago.	No. of survivors for 5 years.	Per cent of survivors remaining free of trouble with their feet. %
Histamin reaction normal	19	100
Dorsalis pedis pulse palpable	43	88
Histamin reaction slightly impaired (Grade II)	23	83
Dorsalis pedis pulse not felt	9	56
Histamin reaction markedly impaired (Grade III)	13	38
Histamin reaction shows no wheal in 10 minutes (flare disregarded)	11	27
Dorsalis pedis pulse absent, histamin wheal absent for 10 minutes	5	20

TABLE 3.—COMPARISON OF PROGNOSTIC VALUE OF HISTAMIN REACTION ON THE FEET AND DORSALIS PEDIS PULSATION.

Condition 5 years ago.	No. of years patients exposed to risk of trouble with feet.	No. of patients who developed ulcers, infection or gangrene.	Per cent of patients who may be expected to develop serious lesions each year.
Histamin reactions normal	106	0	0
Histamin reactions slightly impaired (Grade II)	131	0	0
Histamin reactions markedly impaired (Grade III)	106	8	7.5
Dorsalis pedis pulse palpable	295	6	2.0
Dorsalis pedis pulse not felt	48	2	4.2

Certain features of the data given in the tables have been subjected to statistical analysis.[10] The striking difference between the

outcome of cases with normal and markedly impaired histamin reactions is highly significant.* But minor differences in prognostic value, as that between markedly impaired reaction and absent dorsalis pedis pulse, are not significant in so small a series of cases.

In making a prognosis the judgment should not be based on any single factor. If the information provided by the histamin reaction is supplemented by consideration of the physical findings, the age, and strength of the patient, it is to be expected that the danger of serious trouble with the feet can be foretold with considerable accuracy. Many patients can be reassured. In those threatened, extraordinary efforts to keep the feet from contact with extremes of temperature, particularly the cold of winter, to keep the skin in good condition, to avoid trauma and infection, and to treat the most trivial lesions without delay may do much to further the wellbeing and longevity of these patients.

Summary. In 1928–1929, the peripheral circulation of a series of cases of diabetes was tested by means of the reaction of the skin to histamin. The after histories of 89 of these cases have been followed for 5 years or until their death.

No case having a normal skin histamin reaction on the feet, in 1929, developed any serious trouble with the feet during the subsequent 5 years.

Of the 32 patients giving markedly impaired histamin reactions, in 1929, only 5 survived the 5 years without serious trouble with the feet. Four cases eventually developed gangrene, 4 others developed chronic ulceration or infection requiring hospitalization and 6 have suffered from painful feet without serious lesions.

The skin histamin reaction gives valuable evidence concerning the prognosis of peripheral vascular disease in diabetes mellitus. Considered together with the physical findings, this test provides a simple means of dividing cases of diabetes into a group not immediately threatened with peripheral vascular disease, an intermediate group, and a group in which extraordinary precautions must be taken to prevent the development of serious trouble with the feet.

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* *i. e.*, The probability is less than 5 in 100 that the differences found are due to chance in the selection of the cases.

FATAL ANURIA FOLLOWING BLOOD TRANSFUSIONS. INADEQUACY OF PRESENT TESTS FOR COMPATIBILITY.

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Hemolysis has been the major hazard in blood transfusions since 1667, when hemoglobinuria was first reported following the transfusion of sheep blood into man,[1] until the principles of blood grouping were established by Jansky,[2] in 1907, and by Moss,[3] in 1909. It is now generally believed that severe hemolytic reactions result only from errors in the determination of blood groups. Bordley,[4] in 1931, reviewed 17 cases of major transfusion reactions, in all of which there was oliguria, 11 showed hemoglobinuria and 6 were jaundiced. The author stated: "In not a single case is there complete and satisfying evidence to prove that the blood of the donor was compatible with that of the recipient."

We wish to report 2 fatal transfusion reactions which occurred in November, 1933, because our findings raise a doubt as to the adequacy of the conventional methods of testing for incompatibility.

Case Reports. Case 1.—E. A., female, aged 53, came to this hospital in October, 1931, with carcinoma of the cervix uteri and severe secondary anemia. The carcinoma was treated with radium and Roentgen irradiation. The patient, whose blood was found to be Group IV (Moss), received 2 transfusions within a week from different Group IV donors (S. G. W. and C. W. G.). There was no untoward reaction. Two examinations in 1932 and 3 in 1933 failed to reveal any evidence of neoplasm. In March, 1933, the patient noticed blood in the stools and this continued until November, when she returned to the hospital because of pallor and weakness. Again, no evidence of neoplasm could be found in the pelvis or in the gastroenteric tract. The skin over the lower abdomen was inelastic and presented many dilated venules. The mucosa of the lower bowel was thickened, inelastic and bled easily, but was not ulcerated. It was concluded that the bleeding was due to irradiation endarteritis of the lower bowel.

There was no free hydrochloric acid in the gastric secretion after histamin stimulation. Hemoglobin, 35% (Sahli); erythrocytes, 3,250,000; leukocytes, 4,600 per c.mm. There was some anisocytosis and many microcytes.

October 20, 1933: Transfusion of 400 cc. citrated blood from donor C. W. B. (Group IV, Moss) without cross-matching. The rectal temperature rose to 104.2° F. and there were headache, nausea and vomiting, but no jaundice or hemoglobinuria.

October 30: Hemoglobin, 45% (Sahli); erythrocytes, 3,550,000; leukocytes, 6000 per c.mm. After satisfactory cross-matching with the blood of donor A. L. B. the patient was given 500 cc. of citrated blood. The transfusion was followed by a slight chill, a temperature of 102.8° F. (rectal),

jaundice, albuminuria and hemoglobinuria, but no erythrocytes were found in the urine.

November 1: Capillary resistance test negative; bleeding time (Duke), 6 minutes; coagulation time (capillary tube method), capillary blood, 3 minutes, and venous blood, 5 minutes; prothrombin time (Howell), 4 minutes; hemolysis of erythrocytes began at 0.44% saline and was complete at 0.3%; the clot was normally retractile; blood platelets (Van Allen), 0.4% by volume; hematocrit (Van Allen), 32%; hemoglobin (Newcomer), 8 gm.

TABLE 1.—BLOOD CHEMICAL STUDIES AND URINARY OUTPUT IN CASE 1.

Date, 1933.	Urine.	Van den Bergh (Gibson[18]).	Blood urea N, mg. per 100 cc.	Blood uric acid, mg. per 100 cc.	Blood creatinin, gm. per 100 cc.	Blood CO_2 combining power, vol. %.	Blood chlorid, mg. per 100 cc.
Oct. 30 . .				Transfusion			
Nov. 1 . .	..	4.4 indirect					
12 . .				Transfusion			
13 . .	50	17.4 direct					
14 . .	400	0.9 direct	79.4	6.6	4.0	35.0	
15 . .	600	0.9 direct	86.8	6.6	7.7	34.1	536
16 . .	35						
17 . .	75	...	81.9	6.8	10.0		
18 . .	85						
19 . .	50	...	94.5	...	12.0	26.8	555
			Cystoscopic examination				
20 . .	335	...	100.0	10.0	11.5		
21 . .	*	...	102.0	9.6	12.0	24.0	555
22 . .				Died			

* Incontinent.

November 12: Hemoglobin, 70% (Sahli); erythrocytes, 4,650,000 per c.mm. The washed corpuscles from 500 cc. of citrated blood of donor L. M. F. were given intravenously after compatibility had been established by grouping and cross-matching. Immediately after the transfusion the patient complained of cramps in the right thigh and lumbosacral region, and could not move her leg. There was pain in the abdomen, vomiting, chilliness and the rectal temperature reached 103.2° F. Jaundice became apparent 7 hours after the transfusion. The degree of oliguria can be seen in Table 1. All urine specimens contained hemoglobin and granular casts, but erythrocytes were not observed. Intravenous injections of saline and glucose were given and heat was applied to the kidney regions. Slight generalized edema soon became apparent. On November 17, the tests of November 1 were repeated, with essentially the same results except that hemolysis of erythrocytes began at 0.48% saline. On November 18, cystoscopic examination revealed bloody urine coming from both ureters. The kidney pelves were irrigated with very warm water. Pulmonary edema developed on November 20 and oxygen was administered. Blood (200 cc.) was withdrawn and replaced by saline.[7] The blood of the last donor (L. M. F.) was again cross-matched with that of the patient and no agglutination occurred in 4 hours at room temperature. At the end of 18 hours there was still no agglutination, but some of the donor's corpuscles had disappeared, whereas the recipient's corpuscles were intact. Intracutane-

ous tests on the recipient with the donor's corpuscles and serum were negative. On November 22 (10 days after the last transfusion), the patient died. Permission for necropsy could not be obtained. The urinary volume and blood chemical findings are included in Table 1.

Case 2.—W. B., male, aged 65, was admitted to this hospital, November 8, 1933, because of hemorrhage from a peptic ulcer. He was weak and pale. Hemoglobin, 27% (Sahli); erythrocytes, 1,950,000; leukocytes, 5950 per c.mm. He received the usual treatment, and by November 14 hemoglobin was 35% (Sahli). His blood was found to be Type IV (Moss) and he received a transfusion of 500 cc. citrated blood from G. D. M. without reaction on November 16. Preliminary cross-matching was satisfactory.

On November 25, his blood matched that of J. F. S., another Type IV donor, and he was given 500 cc. of citrated blood from this donor. When about 75 cc. of blood had been given, the patient complained of a cramp in the right hip which was relieved by change in position. The transfusion was resumed and the entire operation was concluded in 75 minutes. About 1 hour later he was nauseated and vomited. The rectal temperature rose to 100.4° F. and he had a slight chill. He passed no urine from the time of transfusion until his death. Fluids were given by vein, subcutaneously and by mouth. The blood corpuscles and serum of J. F. S. and the recipient were again cross-matched and no agglutination was detected microscopically.

Table 2.—Blood Chemical Studies in Case 2.

Date, 1933.	Blood urea N, mg. per 100 cc.	Blood uric acid, mg. per 100 cc.	Blood creatinin, mg. per 100 cc.	Blood CO_2 combining power, vol. %	Blood chlorid, mg. per 100 cc.	Van den Bergh (Gibson[16]).
Nov. 10	14.0	3.1	1.0	58.7	602	
16			Transfusion			
25			Transfusion			
27	62.3	5.5	6.4	58.9	600	
28	80.5	6.5	8.3	56.0	595	0.2 indirect
29	88.9	8.5	10.7			
Dec. 1	125.0	10.0	13.0	45.7	585	
2	141.4	10.0	15.5	35.2		
4	164.0	10.0	14.0	31.5		
5	183.4	10.0	17.6	Died		

On November 29, cystoscopic examination was performed and the renal pelves were washed with very warm water. This did not stimulate the urinary flow appreciably. The patient was drowsy and his muscles twitched occasionally. On December 3, he developed hiccoughs which were relieved by the inhalation of carbon dioxid. On December 5 (10th day after transfusion) he became stuporous and died. At no time was jaundice observed.

The blood chemical studies are included in Table 2.

Necropsy was performed by Dr. C. H. Coughlan. The pertinent findings, submitted by Dr. H. P. Smith, are as follows:

"The liver weighs 1950 gm. No abnormalities are made out in gross. Microscopically, one sees tiny areas of injury at the centers of many of the lobules. In such spots the liver cells are gone and there is hemorrhage, together with a few leukocytes and a few pigment-laden phagocytes. No pigment is seen elsewhere in the liver. There are a few lymphocytes in the portal spaces.

"The two kidneys are similar. Each weighs 250 gm. The capsule strips readily, leaving a smooth surface. No hemorrhages are seen. The cortex appears hyperemic and is about 7 mm. thick. The striations of the

pyramids are unusually distinct. Fine golden-yellow, longitudinal lines are noted in the lower halves of the pyramids. The pelvic mucosa is smooth and pink. Microscopically there are a few old areas of scarring. Elsewhere the glomeruli appear normal. They appear to be entirely free of capillary thrombi. There is widespread injury to the tubules. Some of the convoluted tubules show necrosis of the epithelium. Many of the tubules are lined by low cuboidal epithelium having bluish cytoplasm, like that seen in the late stages of mercuric chlorid poisoning. Throughout the cortex there is extensive edema of the stroma, and as a result the tubules are forced apart. In the lumina of the collecting and convoluted tubules one sees great amounts of reddish-brown granular pigment. A few of the epithelial cells in the cortex contain granules similar in appearance (Figs. 1 and 2).

"Diagnosis: Gastric ulcer. Acute tubular nephritis. Chronic cholecystitis with cholelithiasis. Hyperplasia of the prostate. Generalized arteriosclerosis."

Donors. It is well recognized in practice that some donors give more reactions than others. In our cases, 7 donors were concerned; all were members of the hospital staff and all belonged to Moss's Group IV. They had all given other transfusions. S. G. W., intern, had given about 40 transfusions without hemolytic reactions; C. W. G., intern, had given at least 35 transfusions with no major reactions; C. W. B., associate professor, had given at least 75 transfusions without any major reactions; A. L. B., nurse, had given 1 other transfusion; L. M. F., intern, 7; G. D. M., intern, 6; and J. F. S., intern, 8 transfusions, all without reactions.

Technique. The routine method of transfusion was followed in both cases, except in the last transfusion in Case 1, in which washed corpuscles were given. The blood was diluted with 100 cc. of 2% sodium citrate and a small amount of isotonic saline and administered intravenously by gravity. The solutions were made up and sterilized in the "intravenous laboratory" which supplies materials for use throughout the hospital. In November, 9 other transfusions and, in December, 14 other transfusions were given on the Medical Service with similar solutions and the same personnel. One such transfusion was followed by transient jaundice and the patient died 1½ months later of carcinomatosis. Otherwise, there were no reactions of a serious nature.

Cross-matching was done by microscopic examination of hanging drops of undiluted serum and saline suspension of corpuscles. Both the sera and corpuscles of the donors and the recipient were matched separately.

Comment. Moss stated, in 1910:[5] "Isoagglutination may occur independently of isohemolysis but isohemolysis is probably always preceded or accompanied by isoagglutination." With this statement the majority of workers are in accord,[6] and it is because of this opinion that the routine tests for compatibility have been reduced to agglutination tests in most clinics. However, Moss,[5] himself, observed 3 people whose sera contained hemolysins without agglutinins. In 1919, Kolmer[8] cautioned against the exclusive use of agglutination tests as criteria of compatibility because he had found hemolysins unaccompanied by agglutinins in human sera. Bernheim[9] reported a case of hemolytic reaction without agglutination.

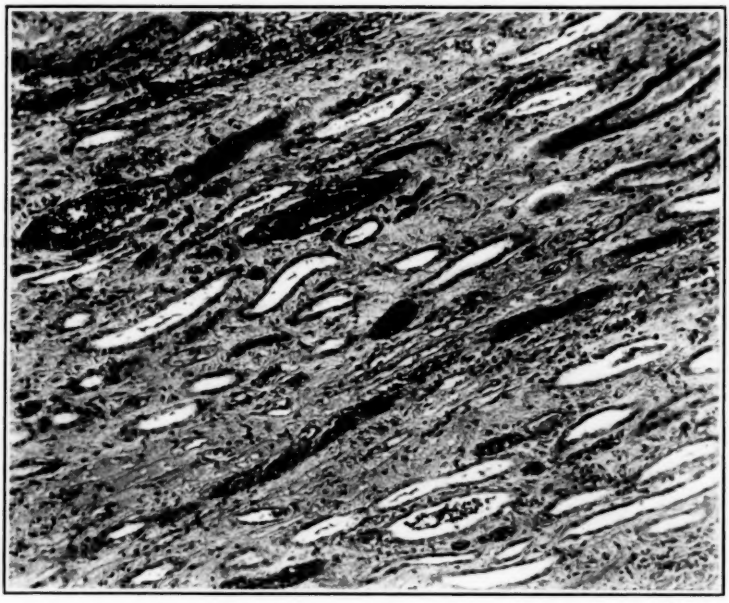

FIG. 1.—Case 2. Photomicrograph (low power) of kidney, showing collecting tubules containing brown pigment, desquamated epithelium and coagulated albumin.

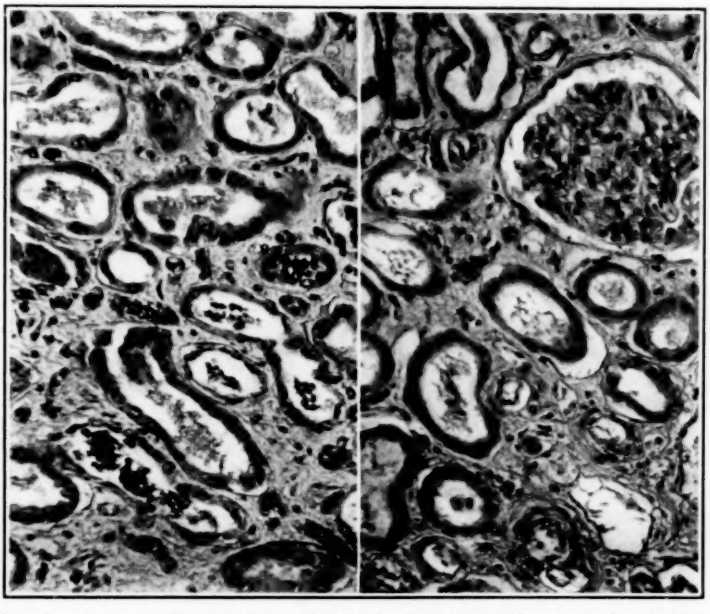

FIG. 2.—Case 2. Photomicrographs (high power), showing necrosis of tubular epithelium and lumina filled with brown pigment, desquamated cells and coagulated albumin. The stroma is edematous. A normal glomerulus is also shown.

Hesse and Filatov[10] reported the case of A. Bodanov, Director of the Institute for Blood Transfusions in Moscow, who died after receiving blood apparently compatible by cross-matching. He had received many previous transfusions without reactions.

Johnson and Conway[14] have recently reported 3 cases of renal insufficiency after transfusions. In 1 the blood was found to be incompatible but in the others there was no sign of agglutination. Incidentally, 1 of these cases had received 4 previous transfusions.

It is obvious that the detection of hemolysis by the hanging drop method is both difficult and uncertain. There is no proof that the sera of the 4 cases cited above or that of our 2 patients would have caused gross hemolysis of the donors' corpuscles *in vitro*. We regret that tests for hemolysis by a test tube method were not done in our cases. At least 4 of the cases mentioned, in which severe reactions occurred without agglutination, had had repeated transfusions. It is possible that these patients developed hemolysins, since in our Case 1 the reactions became progressively more severe with each succeeding transfusion. Certainly if further transfusions are necessary in a patient who has previously suffered a transfusion reaction, tests for hemolysis as well as for agglutination should be done. The influence of repeated transfusions in the production of hemolytic reactions should be investigated further.

The mechanism of the production of the anuria is obscure. Yorke and Nauss,[12] and Baker and Dodds[13] have demonstrated that the excretion of hemoglobin by the kidneys under the proper conditions will produce renal insufficiency in rabbits and that the histologic appearance of the kidneys is similar to the renal lesions in man. Newman and Whipple[14] have shown that hemoglobinuria in dogs causes deposition of hemosiderin in the convoluted tubules of the kidney, as well as in the liver, spleen and lymph nodes and that a minimum renal threshold for hemoglobin is obtained when the tubules have taken up a maximum amount of the iron-containing pigment. Mason and Mann[15] have shown that intravenous injection of hemoglobin has a specific vasoconstrictor effect on the kidney. Hesse and Filatov[10] have recently confirmed this and have shown that the vasoconstriction can be relieved by the transfusion of compatible blood.

The fact that hemoglobin free in the blood plasma is a potent renal toxin seems established. It is as yet not possible to say whether the vasoconstrictor effect or the blocking and destruction of tubular epithelium is the more important.

Bordley[4] has mentioned other possible explanations for transfusion anuria. Any possible toxic effect of the transfused plasma has been ruled out by the fact that our Case 1 received only washed corpuscles. The blood chemical studies in our cases effectively oppose of the theory that loss of blood chlorids or acidosis may be responsible for the anuria.

Obviously further investigations into the pathogenesis of these

unfortunate reactions are necessary before adequate means for their prevention and treatment can be determined.

Summary. Two cases are reported in which death was due to renal insufficiency definitely attributable to transfusions. In neither case could evidence of isoagglutination be found. In 1 case there was questionable evidence of hemolysis. Both patients had received previous transfusions.

Conclusions. 1. The conventional method of testing bloods for compatibility by cross-matching for agglutination only is not sufficient to prevent fatal transfusion reactions.

2. Anuria in the 2 reported cases was not due to loss of blood chlorids or to acidosis.

3. The etiology of the renal damage which results in anuria following transfusions is not yet established.

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THE INFLUENCE OF GLYCIN ON CREATINURIA IN PERIPHERAL NEURITIS.

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The striking changes in creatin metabolism observed in the primary muscular diseases have stimulated new interest in this subject. In 1921, Gibson and Martin[12] found that ingestion of

gelatin increased the creatinuria in progressive muscular dystrophy. Brand and Harris,[8,9,10] demonstrated that glycin was the fraction of gelatin responsible for this change. Milhorat, Techner and Thomas,[18,19,22] and Kostakow and Slauck[14,15] confirmed Brand's observations and also showed that under the influence of glycin the initial increase in creatinuria was followed by a fall in creatin excretion with a concomitant rise in urinary creatinin. With these changes the patients manifested an increased ability to retain exogenous creatin. Beard and Tripoli,[1,2] Mettel and Slocum,[17] and Reinhold *et al.*[20] are among the most recent to report increases in creatin output after glycin feeding.

In myasthenia gravis qualitatively similar changes in creatin excretion have been obtained on feeding glycin by Boothby and his coworkers,[5,6,7] and Remen.[21] Reinhold and coworkers[20] found glycin raised the creatinuria in a case of chronic myositis resembling progressive muscular dystrophy. Harris and Brand[13] also found moderate increases in creatinuria when glycin was fed in Charcot Marie tooth disease and periodic familial paralysis.

The creatinuria existing in the clinical conditions in which secondary atrophies occur responds very slightly or not at all to glycin. The creatin output is not affected in amyotrophic lateral sclerosis, "muscular atrophy" and hemiatrophy, according to Harris and Brand.[13] No changes were noted by Milhorat[19] in amyotrophic lateral sclerosis, severe chronic rheumatism, congenital idiocy, deforming arthritis, spastic paralysis and progressive spinal atrophy. Kostakow and Slauck[14,15] observed no reaction in "secondary atrophies." In contrast with these findings, Beard and Tripoli[1,2] reported a marked increase in creatin excretion, resulting from the administration of glycin in spinal muscular atrophy. Harris and Brand[13] also found a moderate rise in creatinuria in a postencephalitic. The data thus indicate that with these two exceptions, the ingestion of glycin usually has no effect in secondary muscular atrophy. It might, therefore, be expected that glycin would not influence the creatinuria in peripheral neuritis with muscular atrophy. The only instance of plumbism treated in this way is Case 7*a*, studied by Harris and Brand.[13] Daily administration of 10 gm. of glycin for 1 week produced no effect on the creatinuria of this woman. The present case of toxic peripheral neuritis was studied to determine the response to glycin.

Case History.* J. P., Polish, male, aged 53, was admitted to the New Haven Hospital on July 3, 1933, complaining of progressive weakness and pain of the extremities and inability to walk. On May 4 he began to feel sick, feverish and vomited. The next day he was unable to get out of bed and the day after that he felt a soreness in his fingers and feet. The vomiting persisted for 4 days. On May 11, examination by his phys-

* We wish to express our thanks to Dr. L. Greenburg, of the Department of Public Health, who first brought the patient to our attention.

ician revealed severe cough, fever, moist râles at both bases of the lungs and marked ataxia of the legs. His abdominal and deep reflexes were normal and there was no tenderness over the nerve trunks. The respiratory symptoms subsided in about 2 weeks, but the ataxia became more severe and pains developed in his hands and feet. Neurologic examination at the Grace Hospital revealed moderate atrophy of the extremities, paresthesias of the finger tips and legs and absence of kinesthetic, stereognostic and vibratory senses in fingers and toes. The tendon reflexes were now markedly diminished and the abdominal reflexes almost absent.

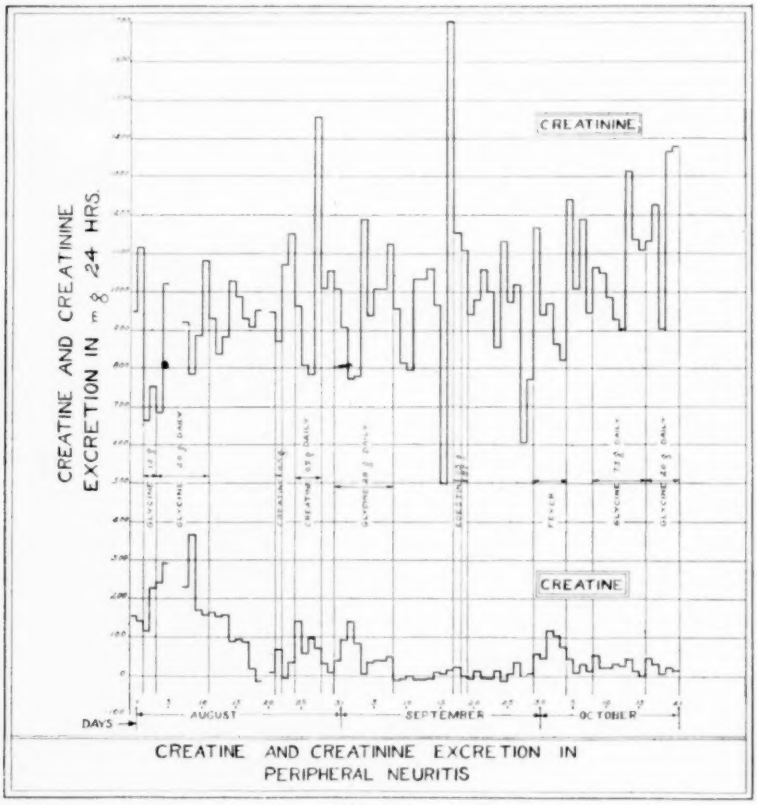

CHART I.

Urinary retention and pyuria were also present. He received mercury succinimid (gr. $\frac{1}{6}$ q.d. for 6 days) and was discharged against advice, unbenefited. He was again seen by his physician about 3 weeks after discharge, at which time ataxia and weakness had so progressed that he was unable to walk or feed himself. He was then referred to the New Haven Hospital for further care. Examination on July 3 revealed an undernourished male with marked atrophy and flabbiness of the extremities. The extensors were more involved than the flexors. Coarse fibrillary twitchings were seen in the arms and legs. The deep tendon reflexes could not be elicited. Weakness and ataxia of all extremities were marked. Sensory examination

revealed a gauntlet and stocking impairment of all superficial sensations, including vibratory sensibility. Deep muscle tenderness was increased. The blood count was: R.B.C., 4,700,000; hemoglobin, 92%; W.B.C., 9800 (polym., 98%; L.M., 7; lymphocytes, 38; eosinophils, 7). The teeth were worn and carious. The cardiorespiratory, gastro-intestinal and genito-urinary systems were essentially negative.

With a tentative diagnosis of peripheral neuritis, search for a possible cause was made. His occupation had been that of mixing and forking fertilizer containing calcium cyanimid, in an almost completely enclosed bin for 3 months previous to his present illness. He had also drunk alcoholic beverages in moderate quantities for a number of years, although for some months previous to his admission his intake had been limited by his financial situation. No other possible contributory agents were noted.

The patient was placed on a liberal diet supplemented with liver, iron and yeast. Shortly before the experiments were begun, all creatin extractives were omitted from the diet which now contained protein to the extent of 90 gm. and had a caloric value of 3000 calories. It was to this basal diet that glycin or other amino acids were added at various times. Physical therapy consisted of Osgood splints on the feet, a heated cradle over his lower extremities, massage and tank bathing.

His course at the hospital was marked clinically by a fairly rapid return of all forms of sensation except vibratory sense, in the upper extremities and then to the lower. The reflexes were slow in reappearing. At the time of discharge motor and sensory power were practically restored in the upper and somewhat less completely in the lower extremities. Diminished sensation persisted in the distal portions of the toes and soles. The triceps reflex had returned and was accompanied by a more definite periosteal radial reflex. The patient was able to walk on crutches or behind his wheelchair when he was discharged improved on October 30.

Experimental Data. Glycin, edestin, glutamic acid and creatin were separately added to the basal diet at intervals and equivalent amounts of protein were removed when edestin was fed. Analyses of total urinary nitrogen (Kjeldahl), sulphur (Benedict[3]), creatinin and creatin (Folin and Benedict[4]) were carried out daily. The Folin-Benedict method may occasionally give small negative values in the absence of creatin. The changes in creatin excretion are charted.

Results and Discussion. Glycin was given at 3 different periods. The first feeding of 20 gm. glycin daily for 11 days caused a prompt but temporary rise in creatin excretion from 0.118 to 0.368 gm. per 24 hours, and then a fall to 0.161 gm. per 24 hours.

When glycin was discontinued the creatinuria gradually diminished to 0. Glycin was fed again a month later for 10 days, this time eliciting a briefer rise in creatin output, from 0.01 to 0.138 gm. per 24 hours and returning to 0.048 gm. per 24 hours. After omitting glycin from the diet it was found that all but a trace of creatin disappeared from the urine. The third time glycin was given (7.5 gm. for 8 days; 20 gm. for 5 days) there was only a slight rise in the creatin excretion, but there was always some creatin in the urine as long as glycin was fed. The patient experienced mitigation of pain and stiffness shortly after the beginning of administration of glycin. During the long interval (August 12 to September

30) between the first and second periods of glycin ingestion, the stiffness in his legs and arms became progressively worse. The neurologic observations made at intervals of 3 weeks indicate progressive but slow recovery, although this improvement cannot be correlated definitely with the short period of glycin feeding. However, as the clinical condition improved, there was a gradual diminution in the extra creatin excreted in response to glycin.

Other amino acids did not yield the same results. No changes in creatin output were observed with edestin (rich in glutamic acid and arginin) and glutamic acid. The feeding of creatin in 0.5-gm. doses resulted in excretion of about 20% of the ingested amount. The elimination of so small a portion of the exogenous creatin may be attributed in part to the earlier ingestion of glycin. Paresthesias were noted during the creatin administration, resembling the observations of Chanutin[11] in progressive muscular dystrophy.

The other urinary constituents did not present the cycle of changes observed with creatin. The inconstant creatinin excretion which will not be described in detail, is similar to that found by Gibson and Martin,[12] and Magee[16] in progressive muscular dystrophy. The deviations in nitrogen and sulphur excretion were not great, these substances tending on the whole to lessen throughout the period of observation.

The appearance of an intercurrent fever during the course of the experiment was accompanied by an increased creatin output. Of particular interest is the fact that the increased creatinuria preceded the elevation of the temperature and persisted a short time after its return to normal.

Summary. A case of toxic peripheral neuritis with atrophy and creatinuria was studied. Daily analyses were made of urinary excretion of creatinin, creatin, nitrogen and sulphur. In contrast with other cases of secondary muscular atrophy, but like those with progressive muscular dystrophy and myasthenia gravis, the ingestion of glycin markedly increased the creatinuria. The absence of response to edestin or glutamic acid was also noted.

As the patient's condition improved, the creatinuria decreased and the reaction of glycin correspondingly diminished.

We are grateful to the Staff of the Medical Service of the New Haven Hospital for assisting us wholeheartedly in this study.

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THE EXOPHTHALMOS OF GRAVES' DISEASE. ITS EXPERIMENTAL PRODUCTION AND SIGNIFICANCE.*†

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The chronic bilateral exophthalmos that develops in the course of Graves' disease in about one-third of the cases has attracted the attention of anatomists, neurologists, ophthalmologists, physiologists and pathologists alike and each has contributed to its elucidation as well as to the confusion which at present attends it. The recent independent development of two methods of readily producing exophthalmos experimentally in susceptible animals, namely, (*a*) by the injection of anterior pituitary emulsions or extracts in young ducks (Schockaert[1]) and in young guinea pigs (Loeb and Friedman[2]), and (*b*) by the intramuscular injection of cyanids (preferably methyl cyanid) in young rabbits maintained on a diet of alfalfa hay and oats (fresh green prevents or abolishes the exophthalmos) (Marine *et al.*[3,4]) has made it possible further to advance our knowledge of the cause and mechanism of this form of exophthalmos.

Many of the older theories to explain the exophthalmos of Graves' disease—namely that it was due to the accumulation of fat in the

* Read at the 1933 Medical Fortnight of the New York Academy of Medicine.
† Aided by a grant from the Ella Sachs Plotz Fund.

orbit, or edema and venous congestion, or asthenia and fatty degeneration of the somatic muscles, or myositis—are not now believed to be of primary importance, although they are important secondary and contributing or complicating factors.

We take it as established that the primary or essential cause of the widening of the palpebral fissure, the protrusion of the eyeball and the dilatation of the pupil in the rabbit, rat and guinea pig is an increased tonus of the orbital muscles of Mueller (1858)[5] (M. orbitalis, M. tarsalis sup., M. tarsalis inf.) and the pupillodilator muscle. The M. orbitalis in man and in monkeys is vestigial and on this account it is difficult to explain protrusion of the eyeball in these species by its contraction. Unquestionably in human Graves' disease there is usually some weakness of the somatic muscles. These orbital muscles are composed of non-striated fibers and are innervated by the sympathetic nervous system. Electrical stimulation of the peripheral end of the cut cervical sympathetic trunk in the cat, dog and rabbit (Wagner, 1859[7]) causes widening of the palpebral fissure, protrusion of the eyeball and dilatation of the pupil on that side, provided the superior cervical ganglion is intact. Injections of adrenalin also cause retraction of the lids, protrusion of the eyeball and dilatation of pupils. Unfortunately very little has been added to our knowledge of the anatomical relations and physiology of these muscles since Mueller's work. Because of this we have undertaken such a study in the rabbit where, as first shown by Mueller, these muscles are unusually well developed. In general, however, it may be stated that one group of these muscles extends from about the level of the equator of the eyeball into the upper and lower eyelids (Mueller's tarsal muscles) while the other smooth muscle mass forms a cone-shaped cylinder enclosing most of the orbital contents and extends from the margin of the bony orbit backward toward the optic foramen (MacCallum and Cornell[21]).

The nervous pathway of the sympathetic innervation of the smooth muscles of the eye, as shown by Claude Bernard[8] and many others, is usually represented schematically by ganglion cells in the lateral horn of the spinal cord whose axones emerge at the level of the first and second thoracic segment and end around the ganglion cells in the superior cervical ganglion from which the postganglionic axones extend to the muscle.

In 1909 Karplus and Kreidl[9] showed that stimulation of the hypothalamus in cats lateral and slightly posterior to the infundibulum caused maximum dilatation of the pupil, widening of the palpebral fissure and retraction of the nictitating membrane, thus proving for the first time a true hypothalamic center of the sympathetic. The nervous pathway from the hypothalamus to the lateral horns of the spinal cord is not known.

Our interest in exophthalmos was renewed in the fall of 1931,[3] when, following the daily intramuscular injection of 0.05 to 0.1 cc.

of methyl cyanid into prepuberal rabbits maintained on a diet of alfalfa hay and oats, there was a progressive development of bilateral exophthalmos beginning in some cases as early as the 3d week after starting the injections, while in others it began as late as the

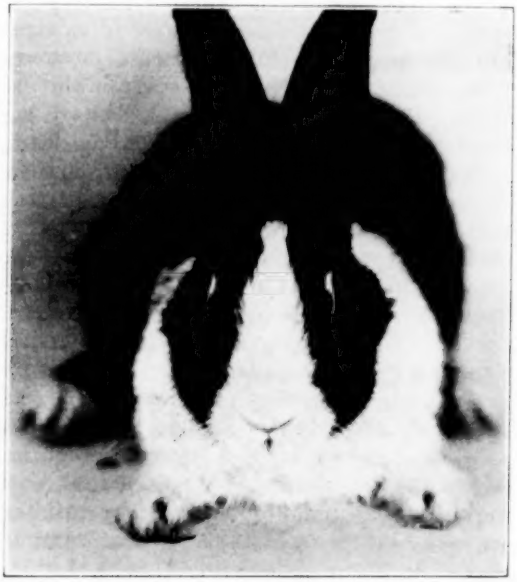

FIG. 1.—Frontal view. Rabbit 1-1339, male, at the age of 117 days and after receiving daily injections of acetonitril in doses of 0.05 to 0.1 cc.

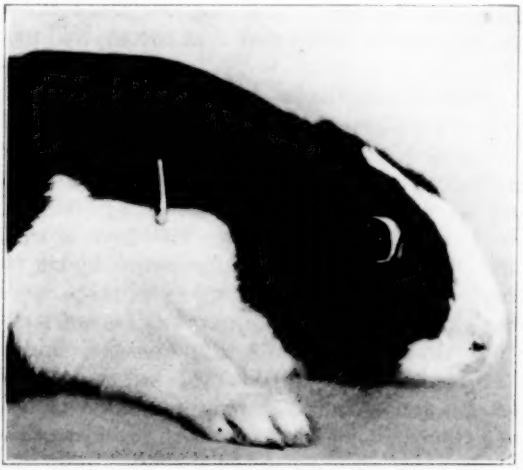

FIG. 2.—Lateral view, same rabbit.

3d month (Figs. 1 and 2). It was much more easily produced in males than in females, and some rabbits of both sexes, but more commonly females, failed entirely to develop exophthalmos in this time period. Adult rabbits of both sexes are quite resistant. Of the two breeds of rabbits we have used, the Dutch strain is much more susceptible than our common gray strain. Along with the development of the exophthalmos there were often signs of precocious sexual development, particularly after thyroidectomy.

The most important association, however, of the exophthalmos was with goiter. Only those rabbits developed exophthalmos which also developed thyroid hyperplasia, showing clearly that there was a close relation between the degree of thyroid insufficiency as indicated by the goiter and the development of exophthalmos. With this fact established, we tried the effect of methyl cyanid on rabbits after thyroidectomy,[10] and found that the exophthalmos was more easily produced and more marked in such animals than in animals with the thyroid intact. (The probable explanation of this will appear later.) This finding indicated that the thyroid hormone had nothing to do with the cause of the exophthalmos. Schockaert and later Loeb and his coworkers had shown that pituitary extracts also caused exophthalmos in young ducks and young guinea pigs respectively. Our experience with cyanid exophthalmos after thyroidectomy led us to suspect that the thyroid likewise had nothing to do with the exophthalmos produced by pituitary extracts. We, therefore, removed the thyroid gland from a number of guinea pigs and injected a potent preparation (Loeb) of the thyrotropic factor. As marked (and usually earlier) exophthalmos was obtained in the thyroidectomized guinea pigs as in the control pigs with intact thyroids.[11] It now appeared obvious that the exophthalmos was brought about by the stimulating action of the thyrotropic factor of the anterior pituitary and that the thyroid gland took no positive part in its causation.

As to the mechanism of the production of exophthalmos by cyanid and diet it is our opinion that cyanid anoxemia aids in bringing about a deficiency of some hormone which stimulates some hypothalamic center which in turn stimulates the anterior pituitary to excrete an increased amount of thyrotropic factor which directly through the blood stream stimulates the thyroid cells and also independently of the thyroid stimulates the higher sympathetic center in the hypothalamus controlling exophthamos. This stimulation of the sympathetic center apparently becomes effective only when the thyroxin content of the thyroid is becoming exhausted. The fact that removal of the superior cervical sympathetic ganglion abolishes exophthalmos caused by methyl cyanid or by the thyrotropic factor, whereas it makes the smooth muscles of the eye more sensitive to adrenalin is further proof that the thyrotropic hormone causes the exophthalmos by acting through a nervous mechanism.

Methyl cyanid also causes an increased output of adrenalin but this is not sufficient to cause exophthalmos in animals with the cervical sympathetic cut or even with the superior cervical ganglion removed.

With this explanation of the mechanism of exophthalmos we can understand why large parenchymatous goiters alone or thyroidectomy alone (Gley[12]) sometimes causes exophthalmos in young rabbits (we have also observed this phenomenon) and why thyroidectomy plus cyanid nearly always hastens the onset of and increases the degree of exophthalmos in immature rabbits. Thyroidectomy, as first shown by Rogowitsch[13] and confirmed by most subsequent observers, is the most potent physiologic stimulus to the anterior pituitary as indicated by the degree of enlargement of the anterior pituitary. Thyroidectomy stimulates the anterior pituitary to excrete more thyrotropic hormone because of the depression of oxidation processes, and if this metabolism depressant is combined with another powerful depressant of oxidation processes (cyanid) we get the earlier onset of and the more severe types of exophthalmos.

Finally there are some practical considerations that are of interest and importance. It has been known since partial thyroidectomy was first introduced into the therapy of Graves' disease that cases of Graves' disease occasionally develop exophthalmos after partial thyroidectomy, and second that exophthalmos existing at the time of operation often was made worse by thyroidectomy[14,15,16]. The more recent subtotal thyroidectomies have undoubtedly further increased the incidence of postoperative exophthalmos. On the basis of our experimental work this could be explained by the increased thyroid insufficiency caused by the subtotal thyroidectomy which in turn calls forth a greater pituitary response.

The only medical treatment that has been found of benefit is the administration of iodin and desiccated thyroid. This, however, has not been very successful, as is indicated by the literature reports. Our attempts to cure the experimental exophthalmos of rabbits with iodin and desiccated thyroid administration, likewise, have been unsuccessful. On the other hand, it is easily prevented in rabbits. If 1 to 2 mg. of iodin are given weekly during the period of methyl cyanid administration no thyroid hyperplasia (goiter) develops and therefore no exophthalmos develops.

The most hopeful means of controlling the exophthalmos of Graves' disease at present available appears to be by prevention. By preventing goiter in general we will certainly lessen anterior pituitary stimulation and thereby lower the incidence of exophthalmos. This has already been proven in the state of Michigan where, following Kimball's introduction of goiter prevention about 1920, there has been a sharp decrease in the incidence both of endemic goiter and Graves' disease (McClure).

The only other general method of attempting the cure of exoph-

thalmos is by dividing the cervical sympathetic or removal of the cervical ganglia as introduced by Jaboulay,[18] Jonnesco[19] and others. Dividing the cervical sympathetic trunk only partially reduces the exophthalmos in rabbits, even in the earlier and uncomplicated stages. Removal of the superior cervical ganglion completely abolishes exophthalmos produced in rabbits by cyanid administration, at least during the first 2 or 3 months of its existence. It would probably be ineffective in the long-standing human cases where marked asthenia, degenerative and inflammatory changes have developed in the somatic muscles. If it were possible to divide the postganglionic fibers supplying the Mueller muscles only, the operation would be beneficial.

Summary. It may be stated that chronic and progressive exophthalmos can now be readily produced in immature animals of susceptible species by injecting pituitary extracts and by the injection of cyanids (preferably methyl cyanid) into rabbits maintained on a diet of alfalfa hay and oats. Both these means of production depend upon 2 factors: (1) upon the thyrotropic hormone of the anterior pituitary, in the one case by passively supplying it and in the other by stimulating the pituitary to produce it, and (2) upon the existence of a relative thyroid insufficiency. The maintenance of a normal thyroid by iodin or thyroxin administration prevents the cyanid and the pituitary extract exophthalmos. This indicates that normally there is a delicate physiologic balance between the thyroxin needs and the thyrotropic hormone. As regards therapy, iodin and desiccated thyroid appear to be the only logical remedies at present available but in neither the human Graves' disease nor in the experimental exophthalmos of rabbits are the results very promising.

The future outlook for controlling this deformity by prevention and even of curing individual cases, however, is far from hopeless. In the first place it can be prevented by iodin or by desiccated thyroid. In the second place it is our opinion that as the nature of Graves' disease is further unravelled it is quite probable that the natural cause (which we believe is due to a deficiency of some hormone of suprarenal cortex and gonad origin) of the stimulation of the midbrain centers occurring in Graves' disease which stirs the anterior pituitary to increased activity will be found and that a hormonal therapy may become available—a hormone probably of suprarenal cortex or gonad origin.[21]

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BOOK REVIEWS AND NOTICES.

TUBERCULOSIS IN THE CHILD AND THE ADULT. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Clinical Professor of Medicine (Department of Chest) University of Southern California, the School of Medicine; Medical Director, the Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, California. Pp. 611; 85 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $8.50.

THIS book encompasses in convenient bulk an adequate description, for the sanatorium physician or the physician in private practice, of the diagnosis and care of tuberculosis and the scientific principles on which these are founded. It is based on a comprehensive review of recent literature in the fields covered. The opening chapters present sociological considerations and the pathological background. The author holds to the view of endogenous reinfection, as the source of adult disease, which was the dominating view up to a few years ago, but he is conservative and gives consideration to the more recent belief, increasingly accepted in this country, of exogenous infection. There is a good exposition of the development, course and suitable treatment of childhood tuberculosis, with an enlightening set of Roentgen ray reproductions illustrating the resolution of childhood lesions. These would be improved if negative instead of positive reproductions were used. Elsewhere in the book superb negative reproductions, with the densities in white, are employed. The importance of the Roentgen ray in prognosis, as well as diagnosis, is well indicated. In general, physicians seeking sound information on the problems commonly encountered in the care of tuberculosis, will find their questions answered, and in conformity with other standard works on tuberculosis. Additional interest is given to this book by the extended consideration devoted to certain physiological principles, or in the author's term, the "Visceral neurology of tuberculosis," a field that has been largely developed by the author. The book is of great value for its concise assemblage of data on reflex symptoms and signs in tuberculosis previously recorded in a series of publications. In a final instructive chapter of 100 pages the diagnosis and treatment of a considerable variety of cases is illustrated by case reports from the author's experience.

E. L.

THAT HEART OF YOURS. By S. CALVIN SMITH, M.D., Sc.D. Pp. 212; 6 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, $2.

THIS book contains a description of the anatomy and physiology of the heart, and outlines the pathology, signs, symptoms and management of heart disease. It is written for the layman. It is not quite interesting enough in its style to be considered "light reading." It is more of the nature of a textbook. The reader may judge of the validity of the doctrine propounded from these quotations: "The eating of an excess of meat may produce a nephrosis of the kidneys." "The chemical formula of water is H_2O and this oxygen content is a valuable source of oxygen supply." "High blood pressure may be an indication that the individual is developing a resistance to an acute infection." "Sugar is a very powerful dynamic substance. In excess, it can so overwhelm the blood as to produce the coma (deep sleep) of diabetic shock. On the other hand, the diminution of sugars within the blood may so reduce the vitality that a form of sugar called glucose is employed by rectal injection to resuscitate the dying."

After describing the circulation of blood from the left ventricle through the aorta and arterioles to the capillaries, the author states: "Let us

continue with the return trip of vitiated venous blood to the heart. *En route*, the returning blood undergoes purification by passing through those filtration plants called the kidneys." The last chapter, "The Psychology of Reconstruction," is very well done. However, the rest of the book contains so many statements that are either inaccurate or debatable, that a doctor should read it himself before he suggests it for his patients' consumption. F. W.

ALCOHOL: ITS EFFECTS ON MAN. By HAVEN EMERSON, M.D., Professor of Public Health Practice, Columbia University. Pp. 114. New York, D. Appleton-Century Company, 1934. Price, $1.

THIS is a brief résumé of the larger volume, *Alcohol and Man*, published in 1932 under the editorship of the author. It is intended for teachers in the public schools and for students in high school or college, to supply them with modern, authoritative information about a topic the social and economical importance of which is now even greater than ever before. The subject is treated concisely and factually and in non-technical words. The book may well be recommended by physicians to laymen seeking general information about alcohol. C. S.

NOTES ON THE MEDICAL TREATMENT OF DISEASE. By ROBERT DAWSON RUDOLF, C.B.E., M.D. (EDIN.), F.R.C.P., Professor of Therapeutics in the University of Toronto; Consulting Physician, Toronto General Hospital, and Victoria Hospital for Sick Children, Toronto, etc. Pp. 540. Fourth edition. Toronto: The University of Toronto Press, 1934. Price, $4.

THE popularity of this little book, as shown by its reaching the fourth edition, is well deserved. Elementary though its scope, its science is sound and it so well seasoned with that which is the art of medicine that it should be particularly useful to the medical student and the young practitioner. R. K.

LE BARBITURISME AIGU ET LES ANTIDOTISMES GARDENAL (STRYCHNINE, CORAMINE, ALCOÖL) (ACUTE BARBITURATE POISONING AND ANTIDOTES FOR PHENOBARBITAL—STRYCHNINE, CORAMINE, ALCOHOL). By G. CARRIÈRE, Professor of the Medical Clinic of the Hôpital St.-Sauveur, Lille; CLAUDE HURIEZ, Chief of the Medical Clinic; and P. WILLOQUET. Pp. 164; illustrated. Lille: A. Durant, 1934. Price, 30 francs.

THIS monograph deals mainly with the clinical literature on acute barbiturate poisoning (its symptoms, signs, prognosis and pathology) and with a small series of animal experiments in which electrocardiographic tracings were made, the above-named antidotes were tried, and postmortem studies were made of the pathologic lesions. In view of the growing frequency of poisoning by drugs of this group, a publication of this nature would be welcomed by clinicians, but this one is not critical or comprehensive enough to satisfy the need. Nevertheless, it points out certain characteristics of human barbiturate poisoning that are not generally appreciated: fever, usually on the second day; oliguria or anuria, which may persist and cause death from uremia; myosis; pulmonary congestion, pneumonia, acute pulmonary edema; and a large variety of skin lesions, although these are less frequent in acute poisoning than in chronic. The dangerously toxic doses for man are given as 4 gm. of barbital, 3 gm. of phenobarbital, about 7 gm. of dial. In rabbits phenobarbital character-

istically caused congestion and fatty degeneration in the liver and an acute tubular nephritis; the lesions were not modified by treatment with strychnin. Authors' experience with strychnin as an antidote leads them to doubt that a quantitative antagonism exists between it and barbiturates; although it was of some benefit, it did not cause more rapid recovery and it often caused violent convulsions in the midst of phenobarbital coma. They believe coramin is a more promising antidote, but alcohol (30% intravenously) seems best of all. No explanation for this extraordinary effect of alcohol is offered, nor is there any mention of the dangers (thrombosis or embolism, hemolysis, cardiac depression) of intravenous injection of 30% alcohol: it had not been tried on human beings at the time of writing. C. S.

AN INTRODUCTION TO PRACTICAL BACTERIOLOGY. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh, etc., and J. E. MCCARTNEY, M.B., D.Sc., Director of Research and Pathological Services, London County Council, etc. Pp. 504. Fourth edition. Baltimore: William Wood & Co., 1934. Price, $4.

THIS might well be called a handbook of bacteriology. It will prove a valuable aid to the laboratory technician as a clear, concise presentation of the essential routine procedures. The fourth edition with its exposition of improved cultural methods has a place on the reference shelf of every laboratory. The novel presentation of bits of theory along with the technique increases its usefulness for the undergraduate student, and the book would serve very well as a laboratory outline for first courses in bacteriology. D. L.

A SHORT HISTORY OF SOME COMMON DISEASES. By DIVERS AUTHORS. Edited by W. R. BETT, M.R.C.S. (ENG.), L.R.C.P. (LOND.), Late Resident Medical Officer, Princess Elizabeth of York Hospital for Children, Shadwell, E., etc. Pp. 211. London: Oxford University Press, 1934. (Price not given.)

THIS "original venture in medical literature" gives, entertainingly but compactly, the important details in the development of knowledge of more than a score of the commoner diseases. The names of such well-known writers as Broadbent, John Fraser, d'Arcy Power, Humphrey Rolleston, R. O. Moon, J. D. Comrie and others guarantee the accuracy of the presentation. One regrets that apparently limitations of space have at times led to a rather categorical listing of events in a book that one would like to have seen twice as large. E. K.

NEW BOOKS.

International Clinics, Vol. 3, Forty-fourth Series, 1934. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 collaborators. Pp. 327; illustrated. Philadelphia: J. B. Lippincott Company, 1934.

Items of especial interest in this number are the two opening articles on the heart with an excellent colored plate of cardiac cyanosis, a short but illuminating statement of a concept of allergy, and an interesting clinicopathologic conference.

Practical Talks on Heart Disease. By GEORGE L. CARLISLE, M.D., Associate Professor of Clinical Medicine, Baylor University, Dallas, Texas. Pp. 153. Springfield, Ill.: Charles C Thomas, 1934. Price, $2.00.

The Compleat Pediatrician. Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital. Unpaged. Durham, N. C.: Duke University Press, 1934. Price, $3.75.

Parasitism and Disease. By THEOBALD SMITH, Director Emeritus of the Department of Animal Pathology, Rockefeller Institute for Medical Research. Pp. 196. Princeton, N. J.: Princeton University Press, 1934, on the Louis Clark Vanuxem Foundation. Price, $2.00.

The Surgical Clinics of North America. Vol. 14, No. 4 (Chicago Number—August, 1934). Pp. 288; 88 illustrations. Philadelphia: W. B. Saunders Company, 1934.

Pathologie der Mitose. By GEORG POLITZER, Privatdozent der Embryologie an der Wiener Universität. Vol. 7 of Protoplasma-Monographien. Pp. 238; 113 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 16.20.

The Cyclopedia of Medicine, Vol. 10. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, M.D., Assistant Editor; Chief Associate Editors, W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. 1167; illustrated with halftone and line engravings, also full-page color plates. Philadelphia: F. A. Davis Company, 1934.

Epidemic Myalgia. Bornholm Disease. By EJNAR SYLVEST, M.D. With a Foreword by DR. TH. MADSEN, Director of the Danish State Serum Institut, Copenhagen. Translated from the Danish by Hans Anderson, M.D. Pp. 155. Copenhagen: Levin & Munksgaard, 1934. Price, D. Cr. 8.—.

Die Werke des Hippokrates. Part 5. Die Winde/Die Heilige Krankheit (Price, Rm. 1.50). Part 14. Die Hippokratischen Lehrsätze (Price, Rm. 2.10). Pp.: Part 5, 65; Part 14, 80. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts, costing ca. Rm. 100, card binding.)

NEW EDITIONS.

A Text-Book of Pathology. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. Pp. 767; 364 illustrations and 2 colored plates. Second edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $8.50.

In the revised and enlarged second edition, many new references and a chapter on diseases of the bones and joints (by Bell) have been added. The good features noticed in our review of the first edition (AM. J. MED. SCI., **181**, 420, 1931), are still present and some shortcomings have been removed. The book continues to be an authoritative statement of the essentials of pathology, with more satisfactory, extended treatment of a few sections.

The Autonomic Nervous System. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-Anatomy in St. Louis University School of Medicine. Pp. 697; 73 illustrations. Second edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $7.50.

A Textbook of Histology. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Associate Professor of Anatomy, University of Chicago. Pp. 662; 530 illustrations, some in colors. Second edition, completely revised. Philadelphia: W. B. Saunders Company, 1934. Price, $7.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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VAGINITIS.

Before attempting to study pathologic lesions of any part of the body it is always well to have a knowledge of the normal histology and physiology of that part. Therefore, some studies on the biology of the vagina are presented.

Varying Vaginal Flora.—Cruickshank and Sharman[1] have observed the bacterial flora and secretions of the vagina at all ages from birth until after the menopause and also during pregnancy. In the virgin there are 4 alternating phases: (1) Soon after birth and for the first 2 or 3 weeks of life simple homogeneous flora of Gram-positive bacilli, known as Doederlein's vaginal bacillus, are established in the vagina in association with a highly acid non-purulent secretion. (2) After the first month and until puberty, vaginal bacterials are sparse and varied while the secretion is scanty or absent and when measurable, is alkalin in reaction. (3) At puberty there is a reversion to the type of flora and secretion found in the first week of life, a condition apparently persisting in the healthy woman until the menopause. (4) Following the menopause, there is a return to the sparse flora and scanty alkalin secretion found in the vagina before puberty. These findings correspond closely with the authors' previous studies on the presence or absence of glycogen in the vaginal epithelium. When glycogen is present, as in the newborn infant and during the reproductive period, the homogeneous bacterial flora and highly acid secretion appear. When it is absent, the secretion is scanty and alkalin and the bacterial flora usually are varied. Obviously the glycogen is being utilized with the consequent production of acid which soon reaches such a concentration that only acid-resistant bacteria, such as Doederlein's bacillus, can survive and multiply. In this way a defense mechanism is produced in the vaginal

cavity capable of preventing the establishment there of foreign or harmful bacteria.

Since the Doederlein bacillus is normally present in the vagina during the reproductive period, Mohler and Brown[2] have used cultures of this organism in the treatment of vaginitis in a small series of cases with encouraging results. The culture, grown in whey, is prepared by mixing ½ ounce with enough sugar of milk to make a thin paste. The mixture is implanted in the vagina after cleansing with dry cotton and a small cotton tampon is then placed in the vaginal introitus. The treatment is repeated once daily either by the physician or patient. After a cleansing douche of plain water, the mixture is injected into the vagina with a soft rubber ear syringe, the patient assuming a reclining position with the hips elevated. Smears of the vagina are made weekly until the Doederlein bacillus can be recovered by culture. All of the patients in this series complained of a leucorrhea which had failed to respond to other methods of treatment, such as cauterization of the cervix and Skene's tubules and the application of antiseptics following thorough cleansing of the vagina. The Doederlein bacillus was absent in every case before treatment was begun. Proof of cure was based on absence of symptoms, the inability to find pus cells in large numbers in stained smears, failure of the vaginitis to return after treatment has been discontinued and finally recovery of cultures of the implanted organisms from the vagina.

Trichomonas Vaginalis Vaginitis.—In recent years much consideration has been given to trichomonas vaginitis. While the disease is frequently found, it is often refractory to all of the numerous treatments advocated. As the organism is a protozoön and as quinin is known to destroy some of the protozoa, it occurred to Sure and Bercey[3] that quinin might be useful in the treatment of such cases. In their small series of 7 cases all have been improved clinically and microscopically by the use of quinin, although 6 of the patients had previously received various treatments without improvement. The treatment consists of the insufflation of 15 grains of quinin sulphate powder into the vagina with a powder blower daily for a few days, checking the effect of the drug on the organisms which as a rule soon disappear. In some cases this was supplemented by the use of 15-grain quinin capsules which the patient inserted into the vagina at night. Under the microscope it was found that when quinin was brought in contact with trichomonads they were immediately thrown into spasm followed by diminishing motility with complete cessation in a short time.

The treatment advocated by Goodall[4] consists of the use of an acid antiseptic in a medium which will slowly dissolve thereby keeping the vagina in a constant bath of antiseptic. These two factors are obtained by using vaginal cones of 1% picric acid. A cone is inserted high up in the vaginal vault on retiring. A lactic acid (1 dram to the quart) douche is taken daily in the morning. After the first treatment with the cone the whole vagina is stained a pale yellow. There is usually a tendency to recurrence following menstruation, but this may be controlled by the above treatment, in fact the treatment may be continued throughout menstruation. His results have been successful in a series of 64 cases in from 5 to 10 days. The pruritus disappears during the

first 3 treatments and the pus is generally absent on the 3d or 4th day Desquamation goes on for some time but by the 10th day the mucosa has taken on a healthy appearance. The treatment may be given during pregnancy except during the last month.

The method of Ruble[5] is based on the principle of osmosis. The trichomonas has a semipermeable cell wall which encapsulates a fluid or semifluid protoplasm. Theoretically a rapid increase in salt concentration in the fluid surrounding the trichomonas should result in its destruction, in the process of establishing osmotic equilibrium. Corroborating this theory by laboratory experiments, Ruble then applied it clinically by having the patients insert 2 magnesium sulphate suppositories (75 grains each) into the vaginal vault night and morning for 3 days and then 2 each night for the next 3 days. On the 7th day there are few pus cells remaining and usually no organisms. If organisms are still present either the amount of magnesium sulphate is increased or copper sulphate suppositories (5 grains) are substituted. Subsequent treatment consists of one suppository nightly until the next menstruation when 2 are inserted each night during the flow. If no organisms are present after the flow, the suppositories are continued every other night during the second month. All treatment is discontinued at the end of the second period, if examination shows no organisms.

Smith[6] treats these patients by the use of a suspension of $\frac{1}{2}$ teaspoonful of sodium perborate powder in a half cup of lukewarm water. In the recumbent position the patient gently injects this freshly prepared suspension into the vagina night and morning and continues the treatment during menstruation. In 2 or 3 days the patient experiences marked relief from symptoms and as a rule speaks of a great lessening of the vaginal discharge. It is his practice at the first examination to instil into the vagina a small amount of 5% mercurochrome on a sponge. If the routine is continued for 1 or 2 months or through 1 or 2 menstrual periods, the patient may stop all treatment and be free from symptoms. The basis on which this treatment is founded is that in cultures the trichomonas is found at the bottom of the test tube and also multiplies under true anaërobic conditions. Furthermore increased oxygen tension is toxic for a number of parasitic species of trichomonads. Sodium perborate when in contact with exudates gives off bubbles of oxygen, though more slowly than hydrogen peroxid.

According to Ayer and Neil[7] trichomonas vaginitis yields readily to treatment based upon the fact that trichomonas vaginalis requires an environment which is acid in reaction. For 5 years they have had unvarying success in the treatment of this disease by a simple form of treatment. Bicarbonate of soda is given by mouth until the urine is alkalin, usually giving 2 or 3 teaspoonfuls daily. After thoroughly cleaning and drying the vagina and cervical canal, the lower cervical canal is packed with powdered sodium bicarbonate and then about 2 ounces of the bicarbonate is packed into the vagina as the speculum is withdrawn. The patient takes a douche the following day using 1 to 2 ounces of soda bicarbonate to 1 quart of warm water and assuming the recumbent position. The "soda pack" gives a burning sensation which lasts for 3 to 5 hours but most women are willing to endure it without sedatives. Relief from burning on urination and vulval irritation occurs within 24 hours from the institution of treatment. Treat-

ments are given on alternate days until the parasites disappear, after which the douches alone are continued until after the second menstrual period. If the patient is then microscopically negative, treatment may be discontinued.

It might be well to call attention to the fact that, in the opinion of some investigators, the trichomonas vaginalis has very little if any etiologic relationship to vaginitis. Thus Hibbert[8] states that it may be found in the vaginal secretions of many women for long periods of time without producing vaginitis. On the other hand in a large percentage of cases having an acute vaginitis where the trichomonas exists, there is an associated predominant growth of a Gram-positive, nonhemolytic, short-chain streptococcus present which is capable of producing an active vaginitis when not associated with the trichomonas. He has found that by repeated vaginal applications of a specific streptococcic bouillon filtrate the active growth of the organisms in the vagina ceases and the vaginitis subsides in spite of the persistence of the protozoön in the secretions. After describing the method of preparation of the bouillon filtrate he states that the method of treatment was uniform. All other methods of treatment were suspended, all douches forbidden and the patient was allowed 1 tub bath daily. In indicated cases repeated cauterization of the cervix was resorted to where cervicitis was present. The vaginal canal was dried with sterile cotton and a large cotton tampon saturated with the bouillon filtrate was packed against the cervix and allowed to remain in place for 12 hours during which time the patient was advised to remain off her feet in order to aid in retaining the fluid in the vagina. The treatment is repeated 2 or 3 times a week until the vaginitis disappears.

Another line of reasoning concerning the rôle of the trichomonas is that suggested by Hesseltine[9] who states that it is well established that patients suffering from trichomonas vaginitis are prone to have recurrences, especially at or following the menses. It is equally known that exacerbations of gonorrheal cervical infections are often related to the menstrual period. By analogy one might argue that the etiologic agents in "trichomonas vaginitis" were bacteria with their foci in the deeper vaginal epithelium or in the cervical glands. Such infections present difficulties in effecting prompt and consistent cures. The most conclusive study in determining pathogenicity of vaginal flagellates would involve freeing the trichomonads from all bacteria, fungi and other infective agents and transplanting them into the vaginas of uninfected women and then being able to recover and identify the organisms after the disease has developed. If strict isolation proves impossible, proof of pathogenicity must rely upon indirect evidence, such as the production of the disease by bacteria commonly associated with the parasites, with the demonstration of the relationship between the bacteria and the trichomonads. Finally it may be shown that neither the flagellates nor the bacteria by themselves are pathogenic, but that one group activates the other. While he believes that "trichomonas vaginitis" is produced by some infective agent, he feels that the pathogenicity of the trichomonas vaginalis has not been proved conclusively. He states that it would seem that the trichomonas is a scavenger and feeds upon bacteria; furthermore it fails to grow on

media in the absence of bacteria, so that presumably an abnormal vaginal flora is a prerequisite for the invasion of the trichomonads.

During pregnancy the presence of the trichomonas may be a very annoying complication. In the Cook County Hospital, Chicago, Crown[10] examined 300 patients during the 9th month of pregnancy and found the trichomonas vaginalis in 50 of 200 white women and in 50 of 100 colored women. The incidence was much greater in nulliparæ than in multiparæ although age is an irrelevant factor. The large majority of the patients had no complaints relative to the presence of the organism. The trichomonas may be found in any kind of discharge but the characteristic type is thin, yellowish and foamy. It does not cause abortion nor increase puerperal morbidity and causes no difficulty in labor unless there is an associated vaginitis.

In the treatment of trichomonas vaginalis vaginitis during pregnancy Glassman[11] has tried many of the numerous methods recommended but at present advises the use of pure crystallin phenol in an acid medium, notably boric acid powder, instead of the usual sodium bicarbonate, as he found that the sodium bicarbonate often produces an irritation. Essential oils are added for their cooling effect. In acute cases the patient is allowed to take daily douches for 1 or 2 weeks which relieves the symptoms and allays the irritation. The vagina is then swabbed with a cotton pledget and the dry powder, mixed with 3 times its volume of boric acid powder, is instilled into the vagina, the patient being instructed to take a douche with warm water the same evening or the next morning. As the phenol content of the douche powder averages from 6 to 8%, it must be mixed with at least 3 times its volume of boric acid powder before it is used dry in the vagina. In a number of patients who harbored the organisms during pregnancy and had no treatment, a spontaneous cure occurred during the puerperium. In 2 cases they remained free from infection until they again became pregnant when the organisms returned.

Trichomonas vaginalis vaginitis *in childhood* is most unusual, in fact it has been said that the organism has never been found before the onset of menstruation. Whether this has anything to do with the biologic condition of the vagina as outlined in the beginning of this review cannot be definitely stated but it is suggestive. Frankenthal and Kobak,[12] however, report 4 cases of trichomonas vaginalis vaginitis during or before puberty. Three of the patients were prepubescent and the other had had only one menstrual period. They found that the local treatment in children is very difficult and unsatisfactory because of the virginal introitus and the infantile state of the genitals. Improvement of local and general hygiene together with a well balanced diet is very beneficial and the 1 patient in this series who was limited to these measures made the most satisfactory progress. The course of this infection in childhood is quite prolonged and it is more difficult to effect a cure than in adults.

Gonorrheal Vaginitis.—The diagnosis of gonorrheal vaginitis is sometimes surrounded with difficulties and in cases of a medicolegal character may be quite hazardous. In a series of 500 consecutive cases at the London County Council clinic at Whitechapel, reported by Mascall,[13] no case was labeled as gonorrhea unless and until pathologic

tests proved the presence of the gonococcus; clinical observations alone were considered insufficient. Cultures produced the highest number of positive results (66.8%). The value of the gonococcus complement-fixation test is second (58.6%), but the corrected figure when the latest technique is used, places this test first with 79.6% positive results. It has a definite place among the diagnostic methods of gonorrhea; but the clinical history and condition must be carefully considered when interpreting the results. In many cases it is indispensable as 142 cases (20.8%) were discovered which otherwise would not have had their true nature revealed. Smears alone, even when stained with Gram's stain, give poor results (45.4%), which is even worse if only methylene blue is used. Whenever possible the three methods should be combined as the results from one method alone may not be dependable.

Gonorrheal Vulvovaginitis in Children.—Schauffler and Kuhn[14] state that the gonococcus requires a "harbor of infection" for its growth and the development of its pathogenic characteristics. In exposed locations it becomes impotent and perishes. Only in the deep recesses such as the glands of Skene and Bartholin, cervical glands or the plicæ of the tubes does this organism find its ideal habitat. Its pathogenic action on the genital apparatus of children is not due to changes in bacteriologic properties or low resistance of the invaded tissues, as has often been stated, but is due to mechanical and developmental differences between the immature and the mature female genitalia. Since the rudimentary Skene's and Bartholin's glands of immature individuals offer no harbor of infection it is not to be expected that infection of clinical importance will occur. Similarly the immature endocervix is practically never infected by the gonococcus because the cervical glands are not present in a form to harbor the organisms and on this account a high degree of immunity is granted to the endometrium and Fallopian tubes. On the other hand the contracted rugose vagina of the immature individual constitutes an ideal harbor of infection and explains the occurrence of a primary vaginitis as the most usual manifestation of gonorrhea in the immature individual. In the adult, the distention and flattening of the vaginal wall with the frequent introduction of bacteria entirely alters the conditions favorable to the development of this organism. From this it may be seen that the most effective means of treating gonorrheal vaginitis in children is achieved through the use of a relatively firm ointment base, injected by a technique which insures the production of sufficient intravaginal pressure to cause the invasion of the ointment into every crypt and corner of the rugose vagina. They advise the use of 1% silver nitrate incorporated in plain anhydrous lanolin. The ointment should not be warm as its quality of firmness facilitates distention of the vagina with the use of mild intravaginal pressure. Furthermore it is more easily and completely retained if cold and has the highest possible affinity for fluids, which makes it a highly effective vehicle for carrying the antiseptic into the moist vaginal wall, in contrast to the usual petrolatum base which is repulsed by moisture. This article is illustrated by Roentgen ray pictures which are very convincing as to the length of time such an ointment will remain in the vagina. (Years ago Gellhorn

of St. Louis suggested the employment of 1% silver nitrate in a more or less solid base and reported good results from same. Moderately good results from this treatment have also been secured by one of the editors—C. C. N.)

In contrast to the above comparatively simple treatment, Peterson[15] details the method which he has found to be efficient. A 1 to 1000 solution of acriflavin hydrochlorid is injected into the urethra until the urine is repeatedly free from pus. The entire vulvar mucous membrane is painted with a 2% solution of mercurochrome and then the vagina is filled with an ointment of 1% mercurochrome in equal parts of vaseline and lanolin and a light pad and T bandage is applied to retain the ointment. A hot sitz bath is given daily for 15 to 20 minutes and the pelvis is baked in carbon lamp appliances from ½ hour to 1 hour daily. Potassium permanganate douches (1 to 10,000) are given if the discharge is excessively purulent or offensive. Silver nitrate is applied to the urethra and vagina twice a week after the first month's treatment. The hymen is incised when necessary to procure efficient drainage. The cervix is inspected through an endoscope and when found to be affected is treated with a 2% solution of acriflavin, 5% mercurochrome or from 2 to 5% solution of silver nitrate. After a month of routine treatment gonococcus mixed vaccine is given in 4 injections: first dose, 0.15 cc.; on 3d day, 0.2 cc.; on 6th day, 0.25 cc.; on 10th day, 0.3 cc. Cod-liver oil is given 3 times daily during the winter months. When 3 or 4 smears are negative for pus as well as for Gram-negative cocci the children are put under observation for 2 or 3 weeks, during which time they are examined every other day until discharged from the hospital after which they are examined every 2 weeks for 2 to 3 months.

While practically all types of treatment of this disease are based upon the use of local antiseptic applications in one form or another, a radically new method of treatment has been suggested by Lewis[16]. It is generally conceded that the gonococcus is a highly selective organism able to exist only in certain tissues. Furthermore vulvovaginitis subsides before the changes of puberty have converted the delicate thin layered epithelium lining the child's vagina to the thicker structure of the adult, in fact, primary infection of the adult vagina is either extremely short-lived or non-existent. With these facts in mind the thought occurred to him that if one were able to change the character of the epithelial lining of the child's vagina, one might reasonably hope to destroy the invading gonococcus by making its habitat unfavorable. Accordingly he began to treat children having gonococcus vaginitis with theelin, the female sex hormone which is responsible for the sex development of the female at the time of puberty. The treatment has been carried out on 8 children with typical severe vaginal infections. No other form of treatment was employed while theelin was being given. The vulvar surface only was sponged with salt solution when it became fouled with vaginal secretions. Four of the patients presented themselves with recent untreated infections, the remainder gave histories of a gonorrheal vaginitis of from 6 to 20 months' duration. In none of these had treatment been given during the 3 weeks preceding the administration of theelin. No local irritation resulted from the administration of theelin nor were there unfavorable general symptoms. The children receiving larger amounts of theelin exhibited hypertrophy

and increased vascularity of the labia majora and minora and of the introitus which resembled the conditions found in the newborn child. In no case did uterine bleeding result from or follow the treatment. During hospitalization of the patients vaginal smears stained by Gram's method were examined in some instances daily, in others every 3 or 4 days. In the majority of the cases vaginal discharge ceased in 1 to 3 weeks after treatment was instituted. At the conclusion of treatment the discharge was absent in all 8 cases and smears were negative for gonococci. Desquamation of epithelial cells in large numbers was usually found in 7 to 21 days, in several instances being so great that cheesy or scaly plugs were extruded from the vagina. In the earlier cases a bit of the lateral wall of the vagina, 3 to 4 cm. above the hymen was removed for microscopic examination before and after theelin injections. For this purpose a miniature tonsil punch was introduced through a peculum, a procedure which caused little pain and proved harmless. Normal control sections were also obtained at autopsies from the vaginas of children of different ages. The normal child's vagina is lined with delicate squamous epithelium 4 to 6 layers in depth. In contrast, the injection of theelin induces in 10 or more days an enormous thickening of the epithelium, there being from 25 to 35 or more layers of vacuolated cells superimposed upon the basement layer. He has found that small doses of theelin given at short intervals are more efficient than larger doses given infrequently and he plans to test the effect of frequent oral administration of the hormone so as to develop a method of therapy more suitable for use in the home. He particularly emphasizes that until the proper dosage of the hormone and the possible deleterious effect of its administration is understood, it should be employed with caution. In his work all the patients received daily either 1, 2 or 3 hypodermic injections of 50 rat units of theelin in the arm or leg.

This work of Lewis has been corroborated by Brown[17] who treated 7 patients who had been receiving other forms of treatment without results 2 or 3 times a week for months and years. He gave daily doses of theelin varying from 50 to 100 units. The smears became negative in 10 days in half the cases and were negative in all of them by the end of 30 days. He also found that none of the children had vaginal bleeding nor any constitutional reactions, while in only 1 did he notice any marked turgescence of the labia and very slight enlargement of the breasts, that child being the youngest in the series and had received the largest number of injections as well as the largest total amount of theelin. These results, which seem to be based on sound biologic principles, offer the hope that this distressing disease may soon be conquered by a relatively short and simple form of treatment.

Vulvovaginal Diphtheria.—According to the literature as reviewed by Wallfield and Litvak[18] vulvovaginal diphtheria in children is rare but should be considered as serious an involvement as the faucial or pharyngeal forms. The clinical picture varies from a mild infection to one of a severe nature with cutaneous gangrene. A gray membrane may form on the inner surfaces of the labia and extend from there to the surrounding structures. All the tissues involved are red, swollen and extremely painful. A fetid vaginal discharge may be present and

the inguinal glands are swollen and tender. Small ulcerations may remain for some time after the disappearance of the membrane. All cases have marked dysuria and pain on walking or moving the legs but there may be no fever. Toxin absorption seems to be slower from the vagina. Local treatment does not seem to hasten negative cultures and it is debatable whether it is of any benefit, although general hygienic cleaning is permissible. They report a case with extension of the membrane across the perineum to the anal region which was treated with antitoxin 20,000 units intramuscularly and 10,000 units intravenously. Although positive cultures were obtained from the nose, throat, vulva, vagina and anal regions, rapid healing of all lesions followed serum therapy. F. B. B.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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COÖPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS.

ONE of the most outstanding contributions to the field of syphilology in recent years has been a coöperative study originally undertaken by the health section of the League of Nations in which five American clinics participated in an investigation of a study of treatment results in early syphilis and in syphilis associated with pregnancy. These

clinics have extended the original study to include a retrospective inquiry into the results of treatment in various other aspects of syphilitic infection. The clinics and their directors were: the University of Michigan (Udo Wile), the Mayo Clinic (Paul O'Leary), Western Reserve University (H. N. Cole), the University of Pennsylvania (J. H. Stokes) and the Johns Hopkins University (J. E. Moore), in association with the United States Public Health Service (Dr. Thomas Parran, Jr., and subsequently Dr. Taliaferro Clark, Assistant Surgeon Generals in charge of the Division of Venereal Diseases, and Lida J. Usilton, Associate Statistician).

The expense of the undertaking was borne by a generous grant from an anonymous donor and subsequently by the Milbank Memorial Fund and the United States Public Health Service. The accumulated, pooled clinical material approximated 75,000 records of patients treated for syphilis and, while individual directors were responsible for the study of certain phases of the problem and for the conclusions reached in their individual studies, all data were submitted to the entire Group for revision and approval prior to publication. All patients had been treated by relatively modern methods and had to be under observation and treatment for not less than 6 months to be included. The aims and plan of the investigation are discussed in detail in *Venereal Disease Information*, **13**, 135, 1932. It will not be possible to abstract here all the conclusions reached in a study approaching monographic proportions so far published, but an attempt will be made to summarize the most.

Early Syphilis, Clinical Manifestations and Diagnosis. Stokes as spokesman for the Group[1] has reviewed a material of 3244 cases of early syphilis including 342 patients with seronegative primary, 585 with seropositive primary, 2252 in the early secondary phase (lesions developing within the first year of infection) and 65 with late secondary syphilis (lesions developing after the first year). It was found that positive darkfield examinations were obtained in 94.4% of seronegative primary syphilis; 90.7% of the genital lesions of secondary syphilis in which a darkfield examination was made; 85.6% in mouth and throat lesions, and 79.3% in cutaneous lesions, including condylomas. Darkfield equipment can therefore be advantageously used in the diagnosis of secondary lesions. Of the total of 3244 early syphilis patients, 10.5% appeared in the seronegative primary stage; 70.4% in the secondary stage with positive blood Wassermann reaction. The blood Wassermann reaction was negative in secondary syphilis in 1% of patients. Alopecia is more frequent in white females than in white males; twice as frequent in the white as in the colored females. Mucosal secondary lesions other than condylomas are 10% more common in white than in colored patients. Condylomas are more frequent in women than in men. Colored females stand much higher than any other type in this particular; suppression of infectiousness in the colored woman is therefore especially important.

Neurosyphilis was clinically recognizable in 1.7% of 2269 patients with early secondary syphilis before treatment was begun; in all cases, an acute syphilitic meningitis with or without cranial nerve palsies. This type of neurosyphilis yields readily to treatment. Of 1747 patients with spinal fluid tests, the fluids were completely normal in 67.3%;

abnormal in 32.7% without reference to the time of the secondary period at which the test was done. The increased cell count is the most frequent abnormality; a specific warning against the practice from the interpretative standpoint of reporting only the Wassermann test on a spinal fluid. Early asymptomatic neurosyphilis as indicated by cerebrospinal fluid examination regardless of time performed or previous treatment occurs in 23.8% of seronegative primary, 29.8% of seropositive primary, 34.1% of early secondary, and 56.1% of late secondary patients. There is a definite relationship between spinal fluid abnormality and the blood Wassermann reaction; the more marked the fluid abnormalities, the more likely is the blood Wassermann to be positive. More than 40% of those whose fluids show a positive Wassermann test, among other abnormalities, are Wassermann fast. The failure of the blood Wassermann reaction in early syphilis to respond in the first 6 months of treatment is an intimation of the presence of asymptomatic neurosyphilis.

Of the 3244 patients, 2.8% had eye complications on admission. Iritis and uveitis form 73.3% of the eye complications; neuroretinitis, 11.1%; keratitis, 11.1%. Colored patients present eye involvement more than 3 times as frequently as white patients, and females have eye lesions oftener than males in both races.

Results of Treatment in Early Syphilis. Stokes[2] found that in a group of 2889 patients with early syphilis satisfactory results, including "cure," are obtained in the following proportions of cases, dependent on the stage of the disease at which the treatment is begun: Seronegative primary, 27.5%; seropositive primary, 23.2%; secondary, first year, 18.4%; secondary, delayed, 29.2%. This represents a superiority of curative outlook of about one-third when treatment is begun in the seronegative primary stage. Relapse and resistiveness to treatment are also less marked in patients beginning treatment in the seronegative primary stage: 13.2%, as compared with 27% in seropositive primary syphilis, 27.8% in secondary syphilis, and 40% in delayed secondary syphilis.

From the material the statement can be made with almost axiomatic force that continuous treatment, whether prolonged or brief and practically regardless of the drugs used, is superior in its results to intermittent or other schemes of treatment. Continuous and intermittent treatment are in their turn both superior to so-called "intensive" treatment (very short arsphenamin courses); and irregular treatment stands throughout the studies as inefficient, productive of relapse and progression, fixed positive serologic tests and unsatisfactory treatment outcomes. At certain points, intensive is little better than irregular treatment. Among cases treated with arsphenamin alone, the continuous method secured the reversal of the blood Wassermann reaction by the end of a year in 91.2%, whereas the intermittent scheme of treatment, with arsphenamin alone and rest intervals of a month or more, secured only 58.5% of reversals, and irregular treatment with arsphenamin alone secured only 9.3% of Wassermann reversals to negative within a year.

There is a definite relationship between resistant positive serologic tests and the tendency to clinical relapse. The total of relapses in

patients always negative or reversed to negative within the first year is only 22.5%, as compared with 48.1% in patients whose tests showed delayed reversal. This statement holds good for any scheme of treatment and for each type of relapse. Sixty per cent of patients undergoing permanent serologic reversal to negative under treatment do so in less than 6 months and 40% in more than 6 months. In the vast majority of cases, failure to secure satisfactory serologic results lies at the door of the rest interval or irregular treatment, rather than any peculiarity of disease or patient.

The factors underlying the fixed positive Wassermann reaction include (1) the stage of the disease at which treatment is begun, difficulty being experienced much more frequently in seropositive primary, secondary and delayed secondary cases than in seronegative primary cases; (2) the occurrence of lapse from treatment from whatever cause. The effect of treatment on the spinal fluid findings is as follows: Slightly abnormal spinal fluids (cell count above 6, increased globulin) is good, whether treatment be much or little. A much greater resistance attaches to greater degrees of abnormality, including the presence of the paretic formula, which type of fluid is much more difficult to reverse than any other markedly abnormal fluid. Of the total number of patients examined, 1.3% proved to have irreversible spinal fluids (42 cases), which is 5.8% of the 730 abnormal spinal fluids.

Early mucocutaneous relapse occurred in 15% of those who received little arsphenamin (that is, 19 or less injections) and in only 2% of those who received 20 or more injections. Central nervous system syphilis is almost 3 times as common in those who received little as in those who got much arsphenamin. Late syphilis as relapse, excepting cardiovascular syphilis, is entirely absent from the "much arsphenamin" group. Progression in the cardiovascular system, however, occurs approximately as frequently in those who receive much as in those who receive little treatment. No evidence appears from the statistical analyses that mass of treatment is in any way injurious to the patient with respect to the outcome of his infection.

Continuous treatment with arsphenamin in preference to neoarsphenamin is the optimum procedure. The weaknesses of neoarsphenamin from the standpoint of its ability to bring about serologic reversal are in part compensated by the use of a heavy metal, and the disparity between the two drugs tends to disappear as the treatment becomes intermittent or irregular. Neoarsphenamin cannot, however, be rated as an ineffective drug. Comparisons between arsphenamin-mercury and arsphenamin-bismuth treatment disclose the latter as the more effective in ultimate results, mucocutaneous relapse occurring in 9.6% of cases with arsphenamin-mercury and 3.6% of cases with arsphenamin-bismuth. Within the first 3 months of treatment the percentage of patients securing Wassermann reversal is practically identical with both bismuth and mercury, whether used with arsphenamin or neoarsphenamin, but with longer treatment (4 to 12 months) there appears to be a distinct advantage for bismuth over mercury with either arsphenamin or neoarsphenamin (41.5% reversals with arsphenamin-bismuth *versus* 29.7% with arsphenamin-mercury, and 39.8% for neoarsphenamin-bismuth *versus* 33.1% for neoarsphenamin-mercury).

Serologic resistiveness is a definite indication of early relapse of a

secondary type (mucocutaneous or ocular), for there were 25.5% relapses of this type among 1282 patients who were serologically resistant, as compared with 5% of 1962 patients with a more satisfactory Wassermann response. The tendency to relapse is vastly increased by intermittent or irregular treatment, with rest periods voluntary or involuntary; and the serologic resistance of the case is an indicator of relapsing tendencies. Relapse is more frequent in younger than in older patients. The notably greater tendency to mucocutaneous relapse when treatment is begun in seronegative primary stage demands increased, not decreased, treatment, or so-called "abortive cures," at this stage. With respect to complications of treatment in early syphilis appraised on a time-treatment basis, reactivity is high where much heavy metal is employed. It is not greatly increased even by vigorous arsenical treatment.

Although neoarsphenamin has the reputation of being less reaction-producing than arsphenamin, the proportion of serious to total reactions with the two drugs in this study stand as 13.4% for arsphenamin, as compared with 22.0% for neoarsphenamin.

The Treatment of Latent Syphilis. Moore[3] was appointed by the Group to review the records of 1936 patients with latent syphilis (clinically non-recognizable syphilitic infection), the diagnosis resting on a positive serologic test or a clean-cut history of infection inadequately treated. The most noteworthy recent clinical advances in this field are the exclusion from the diagnostic category of latency, of patients with early cardiovascular syphilis (simple aortitis), and of patients with asymptomatic neurosyphilis by means of routine spinal fluid examination. A negative spinal fluid in a patient with latent syphilis is a practical guaranty against the subsequent development of neurosyphilis (excepting a more or less purely vascular involvement).

The aim of treatment in latent syphilis is to increase the probability of "cure" or "arrest," and to decrease the probability of clinical progression or relapse, over the probable result if no treatment is given. In addition, treatment aims at the control of the potential infectiousness of the latent syphilitic. Of the patients with latent syphilis, 50% of white males, 70% of white females, 80% of negro males, and 90% of negro females had never received any treatment prior to admission. Less than 2% had received anything resembling adequate modern treatment. This, in part, is attributable to the factor of symptomless infection with syphilis, and in part constitutes a serious reflection on current medical practice in the treatment of early syphilis.

An analysis of clinical results as compared to the plan of treatment employed suggests that continuous treatment, especially if it includes large amounts of heavy metal, offers a slightly better chance of satisfactory results than intermittent treatment, and that the intensive plan of arsphenamin administration (daily injections) is productive of a greatly increased incidence of Wassermann fastness. A special analysis of continuous *versus* intermittent treatment indicates that in early latency continuous treatment is as essential as in early syphilis; in late latency this is no longer so imperative and rest periods probably do no harm. An analysis on the basis of the amount of treatment administered suggests that in latent syphilis maximum results are obtained with about 20 injections of arsphenamin combined with large amounts of heavy metal, the latter prolonged over long periods of time.

When results are compared on the basis of the total duration of observation, it appears that the natural tendency of latent syphilis is toward spontaneous "cure," and that this tendency is markedly enhanced by treatment. If the results in the treated patients followed for 10 or more years are contrasted with the hypothetical outcome in untreated patients with latent syphilis, the probability of a satisfactory outcome ("cure" or "arrest") has been increased from 35 to 85%, the percentage of Wassermann positive but clinically quiescent cases reduced from 35 to 7.5%, and the probability of clinical progression or relapse reduced from 20 to 30% to 2 to 5%. This gain is certainly due to treatment. The clinical outcome is better in early than in late latency (satisfactory results 50.8% as compared with 33.7%), and in both groups better when the patient was seronegative on admission (usually as a result of previous though inadequate treatment) than when the blood Wassermann was positive. Distinctly better clinical results were obtained in females who were pregnant during or after treatment than in females never pregnant. The occurrence of suggestive but not diagnostic signs of cardiovascular or central nervous system involvement in patients with latent syphilis does not appear to carry a greatly increased hazard for the patient.

Clinical Progression and Relapse, Wassermann Fastness and Death. Moore further states[4] that 94 patients of the total 1936 with latent syphilis were observed to develop clinical relapses. The types of relapse observed were: Early infectious relapse in 16; late cutaneous, mucosal, ocular, or osseous lesions in 15; cardiovascular syphilis in 31; neurosyphilis in 30; and visceral (hepatic) involvement in 5. Negroes are much more liable than whites to develop late relapses in skin, mucosa, eye, or bones. Males are much more liable than females to develop early infectious relapse. Of all relapses 72% occurred after 19 or less injections of arsphenamin. Cardiovascular syphilis is the only form of progression or relapse whose incidence is not markedly reduced by the administration of 20 or more injections of arsphenamin. An analysis of early infectious relapse suggests that the plan of treatment for early latency ought to be identical with that for early primary or secondary syphilis, and that the total duration of treatment should be as great.

Approximately 30% of all patients with latent syphilis have irreversibly positive blood Wassermann reactions. The incidence of Wassermann fastness is slightly greater in patients receiving 19 or less injections of arsphenamin (32.6%) than in those receiving 20 or more. It is more common in late than in early latency, in whites than in negroes, and in non-pregnant than in pregnant women. It is suggested that the natural tendency of Wassermann-fast patients is toward the spontaneous development of serologic negativity. Of 26 known deaths among 1936 patients with latent syphilis, only 5 were attributable to syphilitic infection or treatment for it.

The Course of the Blood Wassermann Reaction in Treated Latent Syphilis. Moore and his associates[5] conclude that the Wassermann response to the first course of arsphenamin in late latent syphilis is much slower than that obtainable in early syphilis; in early latency it is intermediate between the two. The rate of reversal of the blood

Wassermann is in direct relationship to the duration of infection. With the Wassermann technique employed, Wassermann reversal is secured by a 6 to 8 injection course of arsphenamin in 85% of patients with early syphilis, in 34% of those with early latency, and 24% of those with late latency.

The composite Wassermann curves of patients with latent syphilis under prolonged continuous treatment (4 courses of arsphenamin over a period of about a year), as compared with a similar group of patients with early syphilis, indicates that in latency almost all of the serologic response to be expected occurs within the first 4 months of treatment; further treatment has little effect from the serologic standpoint. Composite curves of patients treated continuously are compared with those of a similar group treated intermittently in early syphilis, and in early and late latency. These show that, from the serologic standpoint, continuous treatment in early syphilis is essential, in late latency unnecessary. Early latency occupies an intermediate position.

The existence of a provocative Wassermann in latent syphilis is confirmed. Its character differs from that of the provocative Wassermann in early syphilis, in that its rise is slower and less pronounced but longer sustained.

A Critical Analysis of 157 Cases of Cardiovascular Syphilis. Wile, utilizing material studied in the University of Michigan clinic[6] consisting preponderantly of males, points out that there were 30 cases of uncomplicated syphilitic aortitis, 19 of aortitis with heart failure, 73 of aortic regurgitation and 35 of aortic aneurysm. The average duration of infection before cardiovascular involvement was approximately 15 to 20 years. The Wassermann reaction was positive in 73% of patients with aortitis and heart failure and in 96% with aortic regurgitation. Spinal fluid examination in 38% of the total group was positive in from one-fourth to one-half of the cases.

Dyspnea was the outstanding symptom in all cases. The physical findings in the cases of uncomplicated syphilitic aortitis were more or less limited to accentuated aortic second sound, increased retromanubrial dullness, enlargement on percussion and systolic murmur. In aortitis with heart failure, the most frequent physical findings were enlargement on percussion and edema. The Roentgen ray findings showed a positive and presumptive evidence of aortitis in 67% of the uncomplicated syphilitic aortitis group, 73% of the aortic regurgitation group and 90% of the aortic aneurysm group. From 14 to 37% of the cases had received some antisyphilitic treatment prior to the onset of the cardiovascular involvement, but there were practically none which satisfied the present standard of adequate antisyphilitic treatment.

Arsenical Reaction. Cole's[7] review of the problem of arsenical reactions leads him to the following conclusions. Among a total of 177,360 injections of arsenical salts, the relative frequency of reactions was 15 per 1000, 13 of which were mild and 2 severe. Mild reactions observed, in the order of their frequency, were gastro-intestinal, nitritoid, slight skin eruptions, pruritus, and transient kidney irritability. Severe reactions observed, in the order of their frequency, were icterus,

crustaceous dermatitis, ocular damage, hemorrhagic purpura, and a few instances of aplastic anemia, hepatitis, and encephalitis. In early syphilis the rate for mild reactions was 3 times higher than for severe reactions. Severe reactions, however, showed their highest rate in primary syphilis, followed by a lessened incidence in secondary and latent syphilis. Mild arsenical reactions were noted more than twice as often in females as in males in both colored and white, while severe reactions were seen more frequently in the whites without regard to sex. Mild arsenical reactions were more common in the early years of life, while severe types seemed to increase as the patients got older.

For mild reactions the rate per 1000 injections was practically the same for old arsphenamin and neoarsphenamin, somewhat lower for silverarsphenamin, sulpharsphenamin, and bismarsen. The incidence of severe reactions following sulpharsphenamin was 3.5 per 1000, a higher rate than that for arsphenamin or neoarsphenamin due to the proportionally high incidence of crustaceous dermatitis and purpura hemorrhagica. The rate per 1000 for tryparsamid was also high, 3.7, on account of ocular damage with an incidence of 3.2. Severe reactions from old arsphenamin were no higher than from neoarsphenamin. Reactions of either a mild or severe type occurred with the greatest frequency during the first course of treatment and dropped off gradually with each succeeding course. Approximately 5% of the patients were susceptible to 2 or more arsenicals. Three of every 100 cases reacted to 2 arsenical salts, 10 of every 100 reacted to 3 salts, 15 of every 100 reacted to 4, and in a final highly susceptible group 1 of every 4 patients reacted to as many as 5 different arsenical preparations. The best measure found to prevent reactions was to postpone further arsenical treatment at least a month, preferably 3 to 6 months. Changing the type of arsenical salts was the next best preventive measure, and lowering the dose was the third.

Among the deaths there were 8 cases of hemorrhagic encephalitis, 2 of toxic hepatitis (liver atrophy), 2 of aplastic anemia with purpura hemorrhagica, 1 of agranulocytic angina, and 4 of dermatitis exfoliativa. Two of the cases of encephalitis and 1 of the patients with toxic hepatitis also had dermatitis exfoliativa, thus hemorrhagic encephalitis and dermatitis exfoliativa were the two most frequent complications of arsenical therapy of syphilis resulting in death. The fatal instances of encephalitis and of dermatitis exfoliativa came after only a few doses of an arsenical, and usually in cases of early syphilis. The proportion of fatal accidents was far higher after sulpharsphenamin than after any of the other arsenical preparations.

Cole[8] has likewise reviewed the problem of syphilis in pregnancy. The conclusions are so numerous and important that space does not permit inclusion in this review. This phase of the coöperative clinical study deserves special study however by all obstetricians.

Standard Treatment Procedure in Early Syphilis. Stokes has summarized the principles underlying the present-day management of early syphilis.[9] These articles are so replete with pertinent details that they do not lend themselves well to abbreviation and should be read by all physicians who attempt to treat the disease in the most critical stage of its evolution from the standpoint of the individual as well as the public health.

The authors emphasize that the modern system for the treatment of early syphilis must be *continuous;* it must employ an arsphenamin and bismuth, the latter intramuscularly; it must call for not less than 20, and unless special resistiveness is encountered, hardly more than 30 injections of the arsphenamin; and in accordance with the principles generally recognized in the treatment of the disease, the system should call for continued treatment with heavy metal for 1 year after all symptoms and signs of the disease have disappeared. In order to determine this end point, blood tests should be taken at least at the beginning and end of each arsphenamin course and the patient should be warned of the lack of significance of the negative report from the standpoint of the schedule. Weak positives, after a negative has appeared, should be taken as seriously as strong or fully relapsing positives. A spinal fluid examination with Wassermann, cell count, protein estimation, and colloidal gold test should be made before the end of the arsphenamin phase of treatment or the introduction of any rest period (none to be allowed until after the first year). It is understood that such a system can be carried through only with adequate tolerance on the part of the patient, and this tolerance should be conserved in every possible way. If it fails, the case becomes one for consultation. The same system should be employed whether treatment is begun in the seronegative or seropositive primary, or the secondary stage.

All the above articles represent a monographic coöperative effort in syphilology which is a noteworthy achievement in American medicine, and are deserving of critical study by all physicians who attempt to treat syphilis. V. C. G.

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